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# Enantioselective Formation of Cyclopropane Spiroindenes from Benzofulvenes in a Phase Transfer Catalysis System

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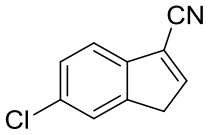
**Contents**

## 1. General methods

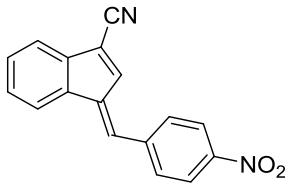
NMR spectra were acquired on a Bruker AVANCE III HD spectrometer running at 400 MHz for $^{1}H$ and 100 MHz for $^{13}C$. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm; $CD_3OD$, 3.31 ppm; DMSO-$d_6$, 2.50 ppm for $^{1}H$ NMR and $CDCl_3$, 77.0 ppm; $CD_3OD$, 49.0 ppm; DMSO-$d_6$, 39.52 ppm for $^{13}C$ NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. $^{13}C$ NMR spectra were acquired in broad band decoupled mode. Mass spectra were recorded on a Bruker Maxis Impact-TOF-MS with electrospray ionization (ESI+) (referenced to the mass of the charged species). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet radiation or $KMnO_4$ stain. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka) was used. Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter, α values are given in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$; concentration *c* in $g \cdot (100\ mL)^{-1}$. The diastereomeric ratio (dr) of products was evaluated by $^{1}H$ NMR analysis of the crude mixture. The enantiomeric excess (ee) of the products was determined by Ultraperformance Convergence Chromatography (ACQUITY UPC2) using Daicel Chiralpak IA, IB, IC, ID columns as chiral stationary phases. Unless otherwise noted, gradient runs were performed with 100% supercritical $CO_2$ for 30 s, then going from 99:1 to 60:40 $CO_2$/solvent over 10 min. Reference samples for $UPC^2$ analysis were prepared following the general method using achiral tetrabutylammonium bromide (TBAB) as catalyst. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

## 2. Synthesis and characterisation of starting materials

1*H*-Indene-3-carbonitrile derivatives and benzofulvenes **1** were prepared following procedures previously described.[1] Characterisation data for previously undescribed substrates is provided below. Ethyl 2-bromo-3-oxobutanoate (**2b**) was synthesized according to a literature procedure.[2]

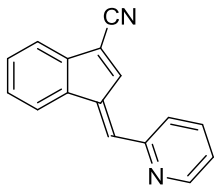



6-Chloro-1*H*-indene-3-carbonitrile was isolated as a brown solid. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.50–7.48 (m, 2H), 7.39 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.30 (t, *J* = 2.1 Hz, 1H), 3.63 (d, *J* = 2.0 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 147.4, 143.3, 138.7, 133.2, 127.6, 124.6, 121.2, 116.6, 114.2, 39.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{10}H_6ClN$ $[M+H]^+$: 176.0262; found: 176.0252.



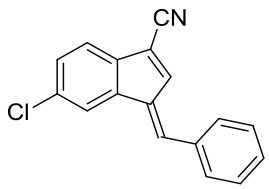
**1c**

(*E*)-1-(4-Nitrobenzylidene)-1*H*-indene-3-carbonitrile (**1c**) was isolated as an orange solid. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.35 (d, *J* = 8.7 Hz, 2H), 7.76–7.72 (m, 4H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.48–7.39 (m, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 147.9, 141.7, 140.5, 138.2, 135.1, 135.0, 132.1 (2C), 131.0, 129.4, 127.6, 124.2 (2C), 120.6, 120.2, 118.8, 114.8. **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{10}N_2O_2$ $[M+H]^+$: 275.0815; found: 275.0816.



**1i**

(*E*)-1-(Pyridin-2-ylmethylene)-1*H*-indene-3-carbonitrile (**1i**) was isolated as an orange solid. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.77 (dd, *J* = 4.6, 1.0 Hz, 1H), 8.56 (s, 1H), 7.77 (td, *J* = 7.7, 1.8 Hz, 1H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.52–7.48 (m, 3H), 7.38 (td, *J* = 7.4, 1.3 Hz, 1H), 7.34 (td, *J* = 7.4, 1.3 Hz, 1H), 7.28 (ddd, *J* = 7.6, 4.7, 1.0 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 154.2, 150.5, 140.0, 138.9, 138.5, 136.9, 135.9, 131.5, 128.9, 127.3, 127.0, 123.7, 120.3, 119.9, 117.3, 115.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{16}H_{10}N_2$ $[M+H]^+$: 231.0917; found: 231.0921.

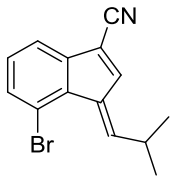


**1n**

(*E*)-1-benzylidene-6-chloro-1*H*-indene-3-carbonitrile (**1n**) was isolated as a brown solid. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.77 (s, 1H), 7.72 (d, *J* = 1.7 Hz, 1H), 7.62–7.59 (m, 3H), 7.53–7.47 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 8.1, 1.8 Hz, 1H). **$^{13}$C NMR (100 MHz,**

[1] B. S. Donslund, R. P. Nielsen, S. M. N. Mønsted and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2016, DOI: 10.1002/anie.201605079.
[2] J. F. Okonya, R. V. Hoffman and M. C. Johnson, *J. Org. Chem*. 2002, **67**, 1102-1108.

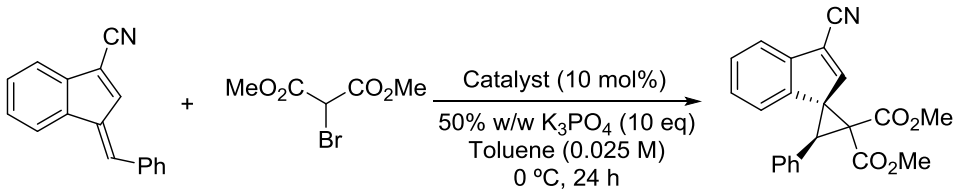
**$CDCl_3$):** δ 137.4, 137.3, 136.5, 136.4, 136.3, 135.2, 133.3, 130.8 (2C), 130.5, 129.2 (2C), 128.2, 121.1, 120.2, 115.8, 115.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{17}H_{10}ClN$ $[M+H]^+$: 264.0575; found: 264.0573.




**1q**

(*E*)-7-Bromo-1-(2-methylpropylidene)-1*H*-indene-3-carbonitrile (**1q**) was isolated as an orange solid. **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.83 (dd, *J* = 10.3, 0.6 Hz, 1H), 7.55 (s, 1H), 7.50 (dd, *J* = 7.8, 2.0 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 3.17–3.08 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 153.8, 141.4, 136.6, 136.3, 132.2, 131.1, 128.3, 119.4, 117.2, 114.8, 112.5, 31.0, 23.1 (2C). **HRMS** (ESI+) *m*/*z* calcd. for $C_{14}H_{12}BrN$ $[M+H]^+$: 274.0226/276.0205; found: 274.0223/276.0204.

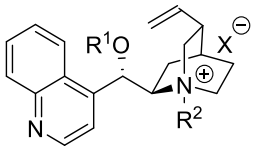
## 3. Phase transfer catalyst screening



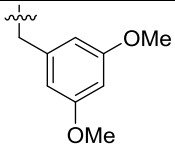
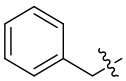
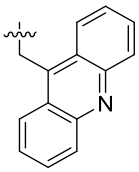
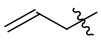
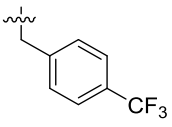
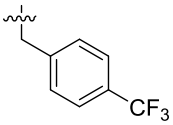

**1a** (1.0 eq) **2a** (1.5 eq) **3a**

In a 4 mL vial containing a stirring bar, the catalyst[3] and benzofulvene **1a** (0.025 mmol, 1 eq) were dissolved in toluene (0.5 mL) and cooled to 0 °C. A solution of $K_3PO_4$ (0.25 mmol) in water (50 µL) was added and, finally, dimethyl bromomalonate (**2a**) (5 µL, 0.038 mmol, 1.5 eq) was added by Hamilton syringe. The yellow reaction mixture was stirred vigorously overnight at 0 °C. After 24 h an aliquot of the organic phase was analysed by NMR[4] and chiral stationary phase UPC[2].

**Table 1.** Screening of cinchonine derived catalysts.[a]

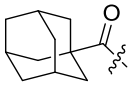
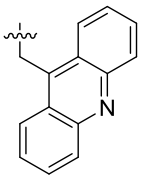
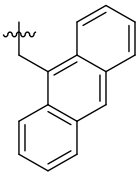
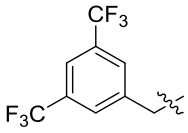
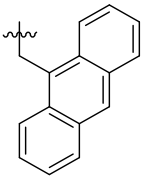
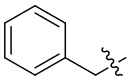
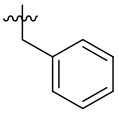
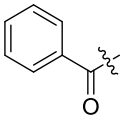
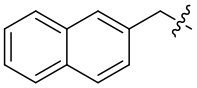
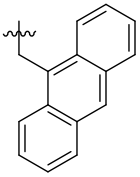
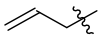
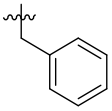
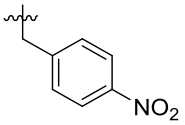
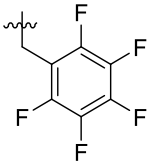
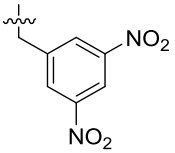



Catalyst

| Entry | $R^1$ | $R^2$ | X | ee (%)[b] |
|---|---|---|---|---|
| 1 | H |  | Br | -16 |
| 2 |  |  | Br | 62 (69)[c] |
| 3 |  |  | Br | 75 (80)[c] |
| 4 | H |  | Br | 72 |

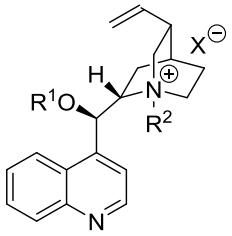
[3] Stock solutions of the catalyst in $CH_2Cl_2$ were applied for screening reactions at 1.0, 0.1 and 0.05 mol% catalyst loading. The catalyst was added first and the $CH_2Cl_2$ was removed *in vacuo*.

[4] In case of incomplete consumption of the benzofulvene, the conversion was determined by evaluating the NMR-signals at 7.69 ppm (one olefinic proton, benzofulvene **1a**) and 4.30 ppm (one proton on the cyclopropane, spiroindene **3a**).

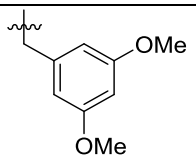
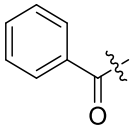
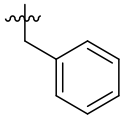
| | | | | |
|---|---|---|---|---|
| 5 |  |  | Br | -19[d] |
| 6 |  |  | Br | 8 |
| 7 |  |  | Br | -9 |
| 8 |  |  | Br | 69 |
| 9 |  |  | I | -4 |
| 10 |  |  | Br | 18 |
| 11 |  |  | Br | 70 |
| 12 | H |  | Cl | n.d. |
| 13 | H |  | Br | n.d. |
| 14 | H |  | Cl | n.d. |

[a] Reactions performed on a 0.025 mmol scale. [b] Determined by chiral stationary phase UPC[2] following filtration of the reaction mixture. [c] Reaction performed at -25 °C. [d] Reaction time was 2 d. n.d. = not determined due to incomplete conversion.

**Table 2.** Screening of cinchonidine derived catalysts.[a]



Catalyst

| Entry | $R^1$ | $R^2$ | X | ee (%)[b] |
|---|---|---|---|---|
| 1 | H |  | Br | -3 |
| 2 |  |  | Cl | -75 |
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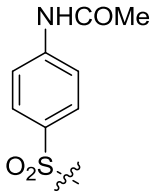
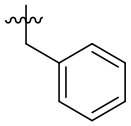
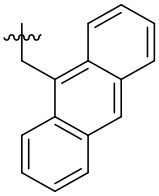
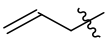
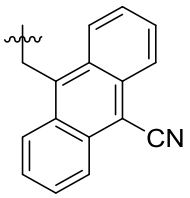
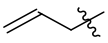
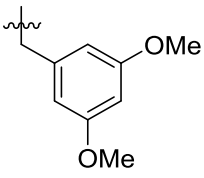
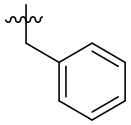
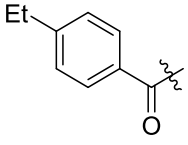
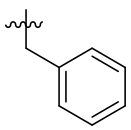
| 4 |  |  | Cl | -59 |
| 5 | H |  | Cl | -21 |
| 6 |  |  | Br | -6 |
| 7 |  |  | Br | -4 |
| 8 | Me |  | Cl | -50 |
| 9 |  |  | Cl | -72 |

| | | | | |
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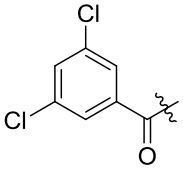
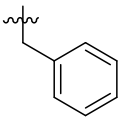
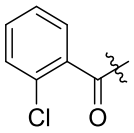
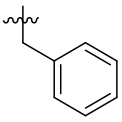
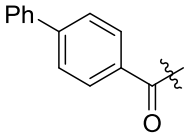
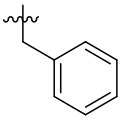
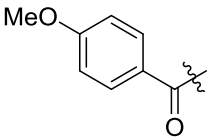
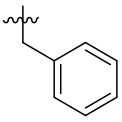
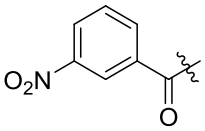
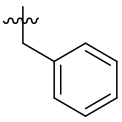
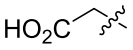
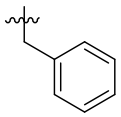
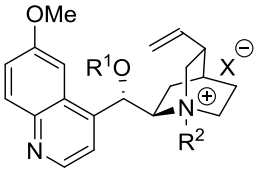
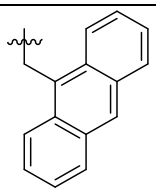
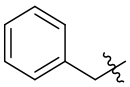
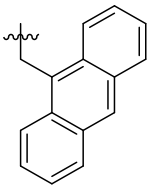
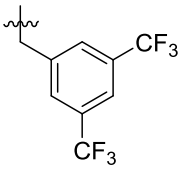
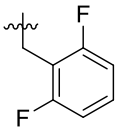
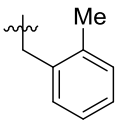
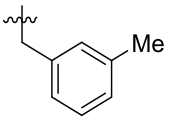
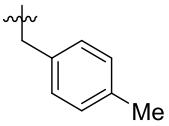
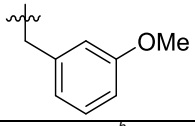
| 10 |  |  | Cl | -65 |
| 11 |  |  | Cl | -66 |
| 12 |  |  | Cl | -60 |
| 13 |  |  | Cl | -75 |
| 14 |  |  | Cl | -55 |
| 15 |  |  | Cl | -58 |

[a] Reactions performed on a 0.025 mmol scale. [b] Determined by chiral stationary phase UPC$^2$ following filtration of the reaction mixture.

**Table 3.** Screening of quinidine derived catalysts.[a]

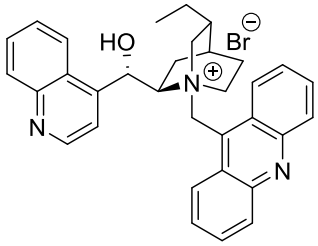
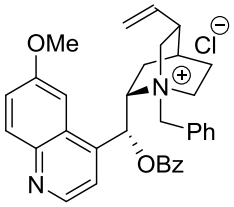
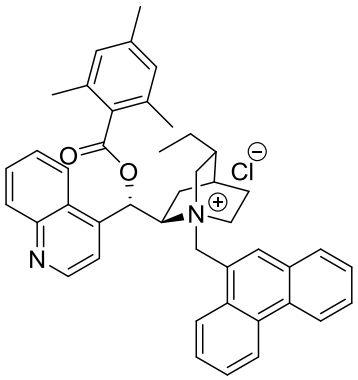
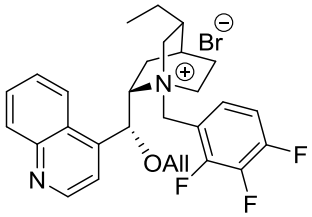
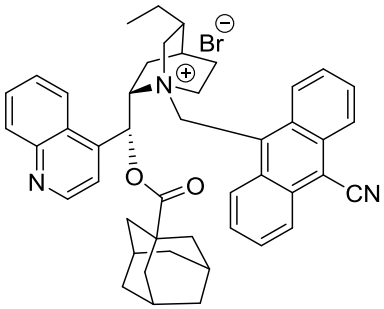
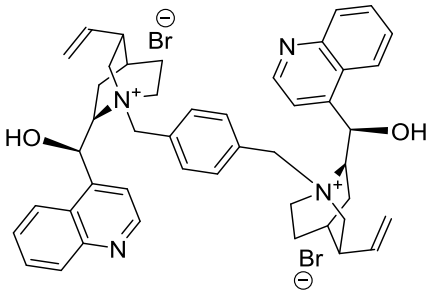


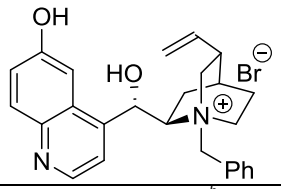

Catalyst

| Entry | $R^1$ | $R^2$ | X | ee (%)[b] |
|---|---|---|---|---|
| 1 | H |  | Cl | 35 |
| 2 |  |  | Br | 53 |
| 3 | H |  | Br | -12 |
| 4 | H |  | Br | 45 |
| 5 | H |  | Br | 71 |
| 6 | H |  | Br | 65 |
| 7 | H |  | Br | 68 |
| 8 | H |  | Br | 66 |

[a] Reactions performed on a 0.025 mmol scale. [b] Determined by chiral stationary phase UPC$^2$ following filtration of the reaction mixture.

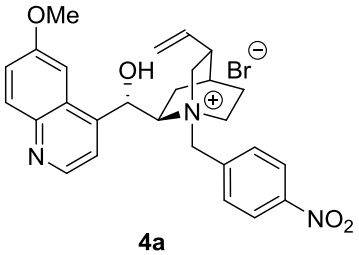
**Table 4.** Screening of other types of cinchona alkaloid catalysts.[a]

| Entry | Catalyst | ee (%)[b] |
|---|---|---|
| 1 |  | 26 |
| 2 |  | -65 |
| 3 |  | <35 |
| 4 |  | -24 |
| 5 |  | 53 |
| 6 |  | -29 |

| | | |
|---|---|---|
| 7 |  | 20 |

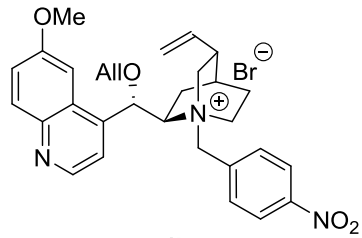
[a] Reactions performed on a 0.025 mmol scale. [b] Determined by chiral stationary phase UPC[2] following filtration of the reaction mixture. [c] Reaction performed at -25 °C.

## 4. Procedure and characterisation of synthesized phase transfer catalysts



**4a**

*N*(1)-*p*-Nitrobenzylquinidinium bromide (**4a**) was synthesized following a literature procedure.[5] Quinidine (4.233 g, 13 mmol, 1 eq) was dissolved in dry THF (100 mL). 4-Nitrobenzyl bromide (2.818 g, 13 mmol, 1 eq) was added while stirring. The reaction mixture was refluxed for 1.5 h. After cooling to rt and stirring overnight, the precipitate was filtered off and dried under vacuum, affording a colourless solid (6.643 g, 94% yield). $[\alpha]_D^{25}$ = +109 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, MeOD-d$_4$):** δ 8.81–8.74 (m, 1H), 8.41 (d, *J* = 8.7 Hz, 2H), 8.05–7.99 (m, 3H), 7.92 (d, *J* = 4.6 Hz, 1H), 7.53 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 6.66–6.56 (m, 1H), 6.10 (ddd, *J* = 17.4, 10.5, 7.2 Hz, 1H), 5.32 (d, *J* = 9.8 Hz, 1H), 5.29–5.27 (m, 1H), 5.24 (d, *J* = 12.6 Hz, 1H), 5.02 (d, *J* = 12.5 Hz, 1H), 4.55–4.45 (m, 1H), 4.11 (s, 3H), 4.08–3.97 (m, 2H), 3.67–3.57 (m, 1H), 3.21–3.08 (m, 1H), 2.73–2.62 (m, 1H), 2.62–2.49 (m, 1H), 2.03–1.95 (m, 1H), 1.95–1.88 (m, 2H), 1.22-1.09 (m, 1H). **$^{13}$C NMR (100 MHz, MeOD-d$_4$):** δ 160.1, 150.6, 148.2, 145.5, 144.8, 137.6, 136.3 (2C), 135.6, 131.8, 127.5, 125.1 (2C), 122.9, 121.7, 118.0, 103.2, 69.6, 67.2, 64.0, 58.5, 56.7, 56.4, 38.9, 28.4, 24.8, 22.4. **HRMS** (ESI+) *m/z* calcd. for $C_{27}H_{30}N_3O_4$ $[M]^+$: 460.2231; found: 460.2236.

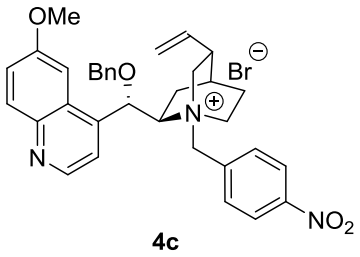


**4b**

*O*(9)-Allyl-*N*(1)-*p*-nitrobenzylquinidinium bromide (**4b**) was synthesized following an adaptation of a known procedure.[6] To a suspension of **4a** (540 mg, 1 mmol, 1 eq) in $CH_2Cl_2$ (10 mL) was added allyl bromide (0.27 mL, 3.2 mmol, 3.2 eq) and a solution of aqueous KOH (0.5 mL, 9.3 M, 4.6 mmol, 4.6 eq). The resulting mixture was stirred vigorously at rt (25 °C) for 4 d. The reaction mixture was diluted with water (5 mL) and extracted with $CH_2Cl_2$ (3x10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC on silica gel (gradient: 5% to 10% MeOH in $CH_2Cl_2$). Dropwise addition of $Et_2O$ to a solution of the product in MeOH afforded the product as a red solid containing minor amounts of impurities (115 mg, 20% yield). $[\alpha]_D^{25}$ = +132 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, MeOD-d$_4$):** δ 8.81 (d, *J* = 4.6 Hz, 1H), 8.43 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 9.3 Hz, 1H), 8.03–7.96 (m, 2H), 7.80 (d, *J* = 4.6 Hz, 1H), 7.65–7.42 (m, 2H), 6.39 (s, 1H), 6.31–6.19 (m, 1H), 6.12–5.99 (m, 1H), 5.50 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.39 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.32 (s,

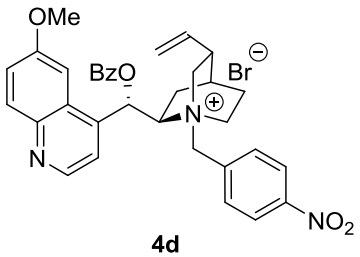
[5] M. Bandini, A. Eichholzer, M. Tragni and A. Umani-Ronchi, *Angew. Chem. Int. Ed.,* 2008, **47**, 3238-3241.
[6] E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.,* **1997**, *119*, 12414-12415.

1H), 5.29 (d, *J* = 6.9 Hz, 1H), 5.11–4.93 (m, 2H), 4.38–4.25 (m, 2H), 4.18 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.11 (s, 3H), 4.07–3.94 (m, 2H), 3.74–3.64 (m, 1H), 3.20–3.06 (m, 1H), 2.74–2.59 (m, 2H), 2.07–1.99 (m, 1H), 1.94–1.85 (m, 2H), 1.37–1.25 (m, 1H). **$^{13}$C NMR (100 MHz, DMSO-d$_6$):** δ 160.2, 150.6, 148.2, 145.3, 141.0, 137.5, 136.4 (2C), 135.4, 134.8, 131.9, 128.4, 125.1 (2C), 123.6, 121.9, 119.5, 118.1, 103.0, 74.8, 71.3, 69.7, 64.4, 58.5, 56.8, 56.6, 38.6, 28.2, 24.5, 23.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{30}H_{34}N_3O_4$ $[M]^+$: 500.2544; found: 500.2553.



**4c**

*O*(9)-Benzyl-*N*(1)-*p*-nitrobenzylquinidinium bromide (**4c**) was synthesized following an adaptation of a known procedure.[4] To a suspension of **4a** (540 mg, 1 mmol, 1 eq) in $CH_2Cl_2$ (5 mL) was added benzyl bromide (0.14 mL, 1.2 mmol, 1.2 eq) and a solution of aqueous NaOH (0.5 mL, 8 M, 4 mmol, 4 eq). The resulting mixture was stirred vigorously at rt (25 °C) overnight. The reaction mixture was diluted with water (5 mL) and extracted with $CH_2Cl_2$ (3x10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC on silica gel (7% MeOH in $CH_2Cl_2$ containing 1% $Et_3N$). Dropwise addition of $Et_2O$ to a solution of the product in MeOH afforded crystals containing an impurity believed to be triethylammonium bromide. Purification by FC on silica gel (8% MeOH in $CH_2Cl_2$) yielded a pale red foam. $[\alpha]_D^{25}$ = +73.2 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, MeOD-d$_4$):** δ 8.84 (d, *J* = 4.6 Hz, 1H), 8.39 (d, *J* = 8.5 Hz, 2H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.94–7.77 (m, 3H), 7.65 – 7.23 (m, 7H), 6.40 (bs, 1H), 5.95 (ddd, *J* = 17.3, 10.6, 6.7 Hz, 1H), 5.25 – 5.03 (m, 2H), 4.83 – 4.61 (m, 3H), 4.23 (t, 1H), 4.17 – 3.88 (m, 5H), 3.57 (t, *J* = 11.4 Hz, 1H), 3.17 – 3.01 (m, 1H), 2.72 – 2.56 (m, 2H), 2.07 – 1.94 (m, 1H), 1.94 – 1.81 (m, 2H), 1.42 – 1.26 (m, 2H). **$^{13}$C NMR (100 MHz, MeOD-d$_4$):** δ 160.3, 150.8, 148.3, 145.4, 140.7, 137.8, 137.4, 136.2 (2C), 135.0, 132.1, 130.4 (2C), 130.2 (2C), 130.1, 128.4, 125.2 (2C), 123.3, 122.2, 118.0, 103.1, 74.0, 72.6, 69.6, 63.9, 58.5, 56.6, 56.3, 38.6, 28.2, 24.4, 22.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{34}H_{36}N_3O_4$ $[M]^+$: 550.2700; found: 550.2700.

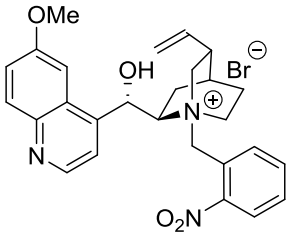


**4d**

*O*(9)-Benzoyl-*N*(1)-*p*-nitrobenzylquinidinium bromide (**4d**) was synthesized following an adaptation of a known procedure.[7] Under an atmosphere of nitrogen, *N*(1)-*p*-nitrobenzylquinidinium bromide (**4a**) (540 mg, 1 mmol, 1 eq), benzoic acid (183 mg, 1.5 mmol, 1.5 eq), and 4-DMAP (12.2

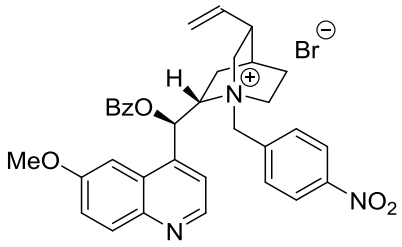
[7] H. Yao, M. Lian, Z. Li, Y. Wang and Q. Meng, *J. Org. Chem.*, 2012, **77**, 9601-9608.

mg, 0.1 mmol, 0.1 eq) were added to a 50 mL flame dried round bottomed flask equipped with a magnet and dry $CH_2Cl_2$ (5 mL). The reaction mixture was cooled to 0 °C, and a solution of DCC (516 mg, 2.5 mmol, 2.5 eq) in $CH_2Cl_2$ (5 mL) was added dropwise over 10 min. The reaction mixture was allowed to reach rt overnight, and full conversion was observed by $^1$H NMR. The reaction mixture was filtered, and from the filtrate the product precipitated after addition of $Et_2O$. Suction filtration yielded **4d** as a colourless solid (470 mg, 73% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +12.1 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, DMSO-d$_6$):** δ 8.73 (d, *J* = 4.6 Hz, 1H), 8.44–8.36 (m, 2H), 8.23–8.16 (m, 2H), 8.12–8.01 (m, 3H), 7.84–7.76 (m, 1H), 7.71–7.63 (m, 3H), 7.57 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.47 (s, 1H), 6.23 (ddd, *J* = 17.3, 10.5 Hz, 6.1, 1H) 5.44 (d, *J* = 10.5 Hz 1H), 5.25 (d, *J* = 17.3 Hz 1H), 5.10 (d, *J* = 12.2, 1H), 4.92 (d, *J* = 12.1, 1H), 4.19 (t, *J* = 9.6 Hz, 1H), 4.15–4.01 (m, 4H), 3.96–3.79 (m, 1H), 3.68 (t, *J* = 11.5 Hz, 1H), 3.00–2.68 (m, 3H), 2.18–2.09 (m, 1H), 1.92–1.62 (m, 3H). **$^{13}$C NMR (100 MHz, DMSO-d$_6$):** δ 164.2, 157.9, 148.5, 147.4, 144.0, 139.5, 137.2 (2C), 135.4 (2C), 135.1, 134.2, 131.6, 129.9 (2C), 129.1, 129.0 (2C), 125.3, 123.7, 122.1, 119.1, 117.4, 102.2, 68.5, 66.6, 62.0, 56.5, 55.9, 54.9, 36.3, 25.6, 22.9, 22.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{34}H_{34}N_3O_5$ $[M]^+$: 564.2493; found: 564.2499.



**5**

*N*(1)-*o*-Nitrobenzylquinidinium bromide (**5**) was synthesized following a literature procedure.[3] Quinidine (1.609 g, 5 mmol, 1 eq) was dissolved in dry THF (50 mL). 2-Nitrobenzyl bromide (1.042 g, 5 mmol, 1 eq) was added while stirring. The reaction mixture was refluxed for 9 h. After cooling to rt overnight, precipitation of the ammonium salt was achieved by addition of $Et_2O$ to the reaction mixture. The precipitate was filtered off and dried under vacuum, affording **5** as a colourless solid (2.253 g, 84% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +52.3 (*c* 1, $CH_2Cl_2$). **$^1$H NMR (400 MHz, MeOD-d$_4$):** δ 8.78 (d, *J* = 4.6 Hz, 1H), 8.34 – 8.23 (m, 1H), 8.09 – 7.99 (m, 2H), 7.99 – 7.83 (m, 3H), 7.52 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.45 (d, *J* = 2.7 Hz, 1H), 6.69 – 6.58 (m, 1H), 6.15 – 6.00 (m, 1H), 5.69 – 5.39 (m, 2H), 5.34 – 5.22 (m, 2H), 4.56 – 4.44 (m, 1H), 4.16 (s, 3H), 4.09 (t, *J* = 9.7 Hz, 1H), 3.87 – 3.74 (m, 1H), 3.66 – 3.48 (m, 1H), 3.23 – 3.08 (m, 1H), 2.67 (q, *J* = 8.7 Hz, 1H), 2.59 – 2.48 (m, 1H), 2.02 – 1.73 (m, 3H), 1.19 – 1.05 (m, 1H). **$^{13}$C NMR (100 MHz, MeOD-d$_4$):** δ 160.3, 152.6, 148.2, 145.5, 144.8, 138.1, 137.7, 135.3, 133.7, 131.8, 127.6, 127.4, 123.7, 122.8, 121.5, 118.0, 102.1, 70.0, 67.1, 60.3, 57.7, 57.1, 56.7, 39.1, 28.2, 24.8, 22.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{27}H_{30}N_3O_4$ $[M]^+$: 460.2231; found: 460.2242.

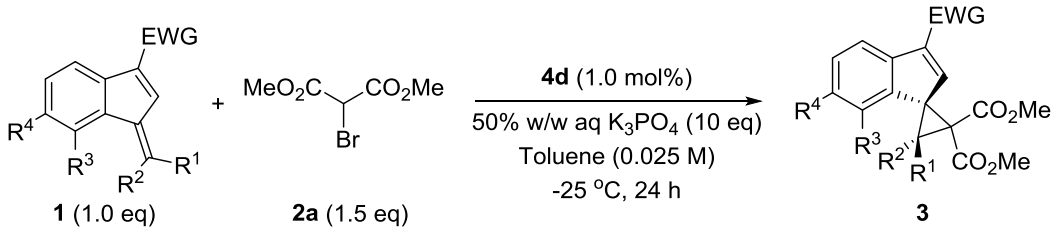



**6**

*O*(9)-Benzoyl-*N*(1)-*p*-nitrobenzylquininium bromide (**6**) was prepared following the same procedure as for **4d** (91 mg, 14% yield). $[\alpha]_D^{25}$ = -16.7 (*c* 0.5, $CH_2Cl_2$). **$^1$H NMR (400 MHz, MeOD-$d_4$):** δ 8.75 (d, *J* = 4.7 Hz, 1H), 8.45–8.38 (m, 2H), 8.37–8.32 (m, 2H), 8.12 (d, *J* = 9.3 Hz, 1H), 7.98–7.91 (m, 2H), 7.84–7.77 (m, 2H), 7.73–7.60 (m, 4H), 7.51 (d, *J* = 2.6 Hz, 1H), 5.82 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.53 (d, *J* = 12.7 Hz, 1H), 5.23–5.11 (m, 2H), 4.30–4.20 (m, 1H), 4.09 (s, 3H), 4.06–3.97 (m, 1H), 3.71–3.46 (m, 3H), 2.91–2.72 (m, 2H), 2.57–2.45 (m, 1H), 2.35–2.26 (m, 1H), 2.14–1.95 (m, 2H), 1.40–1.29 (m, 1H). **$^{13}$C NMR (100 MHz, DMSO-$d_6$):** δ 164.3, 157.8, 148.6, 147.5, 144.0, 139.8, 137.8, 135.4 (2C), 135.1, 134.2, 131.7, 129.7 (2C), 129.2 (3C), 125.0, 123.8 (2C), 122.1, 118.9, 117.0, 101.8, 68.2, 67.1, 62.2, 59.4, 55.7, 50.6, 37.0, 26.1, 24.3, 21.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{34}H_{34}N_3O_5$ $[M]^+$: 564.2493; found: 564.2500.

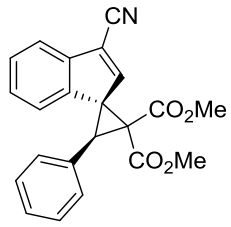
## 5. General procedure for the organocatalytic reaction

### 5.1. Asymmetric synthesis of chiral cyclopropane spiroindenes 3



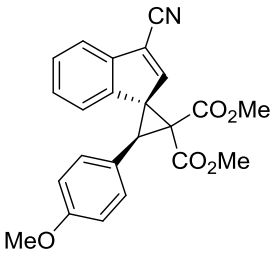

In an 8 mL vial containing a stirring bar, the benzofulvene **1** (0.2 mmol, 1 eq) and catalyst **4d** (1.3 mg, 1 mol%) were dissolved in toluene (4 mL) and cooled to -25 °C. A solution of $K_3PO_4$ (2 mmol) in water (0.4 mL) was added and, finally, dimethyl bromomalonate (**2a**) (40 µL, 0.3 mmol, 1.5 eq) was added by Hamilton syringe. The yellow reaction mixture was stirred vigorously overnight at -25 °C. Full consumption of the benzofulvene was indicated by a colourless reaction mixture. The phases were separated and the aqueous phase was extracted with $Et_2O$. The combined organic phases were concentrated and purified by FC on silica gel.

**5.2. Characterisation of cyclopropane spiroindenes 3**



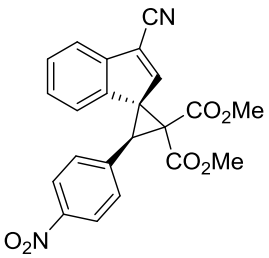

**3a**

Dimethyl (1*R*,3*S*)-3'-cyano-3-phenylspiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3a**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +52.4 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.69 (s, 1H), 7.64 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.46 (td, *J* = 7.6, 1.0 Hz, 1H), 7.35–7.28 (m, 4H), 7.17–7.09 (m, 3H), 4.30 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.2, 165.6, 146.6, 140.3, 139.2, 132.4, 129.0 (2C), 128.6 (2C), 128.2, 128.2, 126.9, 121.0, 119.9, 115.5, 114.4, 53.2, 53.2, 50.9, 46.8, 41.8. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{17}NO_4$ $[M+H]^+$: 360.1230; found: 360.1235. **UPC$^2$**: IA, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.80 min; $t_{minor}$ = 2.64 min.



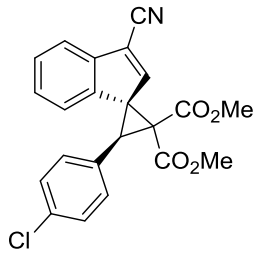

**3b**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(4-methoxyphenyl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3a**) was isolated as a colourless foam by FC on silica gel (10:90 – 20:80 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +0.7 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.69 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.45 (td, *J* = 7.6, 0.9 Hz, 1H), 7.30 (td, *J* = 7.7, 0.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.08–7.03 (m, 2H), 6.87–6.80 (m, 2H), 4.24 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 166.2, 165.7, 159.3, 146.8, 140.5, 139.2, 130.2 (2C), 128.1, 126.9, 124.3, 121.0, 119.9, 115.4, 114.5, 114.0 (2C), 55.2, 53.2 (2C), 51.2, 47.0, 41.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{19}NO_5$ $[M+Na]^+$: 412.1155; found: 412.1155. **UPC$^2$**: IC, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.84 min; $t_{minor}$ = 2.93 min.



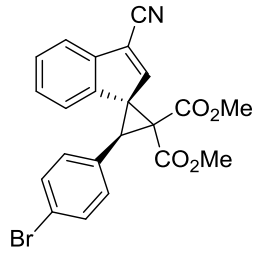

**3c**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(4-nitrophenyl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3c**) was isolated as a colourless foam by FC on silica gel (15:85 – 20:80 EtOAc:pentane). $[\alpha]_D^{25}$ = +6.2 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.66 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.61 (s, 1H), 7.49 (td, *J* = 7.6, 1.0 Hz, 1H), 7.37–7.31 (m, 3H), 7.10 (dt, *J* = 7.7, 0.8 Hz, 1H), 4.28 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 165.7, 165.4, 147.6, 144.7, 139.8, 139.7, 139.0, 130.1 (2C), 128.6, 127.3, 123.8 (2C), 121.3, 119.8, 116.8, 114.0, 53.5, 53.4, 50.2, 46.7, 40.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{16}N_2O_6$ $[M+H]^+$: 405.1081; found: 405.1089. **UPC$^2$**: IA, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.81 min; $t_{minor}$ = 2.95 min.



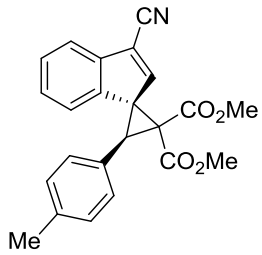

**3d**

Dimethyl (1*R*,3*S*)-3-(4-chlorophenyl)-3'-cyanospiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3d**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +6.9 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.64 (m, 2H), 7.46 (td, *J* = 7.6, 0.9 Hz, 1H), 7.34–7.27 (m, 3H), 7.13–7.05 (m, 3H), 4.22 (s, 1H), 3.72 (s, 3H), 3.67 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 166.0, 165.5, 145.9, 140.2, 139.2, 134.3, 131.0, 130.4 (2C), 128.9 (2C), 128.4, 127.1, 121.2, 119.9, 116.0, 114.3, 53.4, 53.3, 50.7, 46.8, 41.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{16}ClNO_4$ $[M+H]^+$: 394.0841; found: 394.0845. **UPC$^2$**: IA, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.44 min; $t_{minor}$ = 2.56 min.



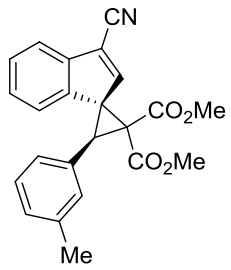

**3e**

Dimethyl (1*R*,3*S*)-3-(4-bromophenyl)-3'-cyanospiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3e**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = -9.6 (*c* 0.5, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.66–7.61 (m, 2H), 7.49–7.43 (m, 3H), 7.31 (td, *J* = 7.7, 1.1 Hz, 1H), 7.10 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.05–7.00 (m, 2H), 4.19 (s, 1H), 3.72 (s, 3H), 3.67 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 165.9, 165.5, 145.8, 140.1, 139.1, 131.8 (2C), 131.5, 130.7 (2C), 128.3, 127.0, 122.4, 121.1, 119.9, 116.0, 114.2, 53.3, 53.3, 50.6, 46.7, 41.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{16}BrNO_4$ $[M+H]^+$: 438.0335/440.03115; found: 438.0337/440.03118. **UPC$^2$**: IA, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.58 min; $t_{minor}$ = 2.74 min.



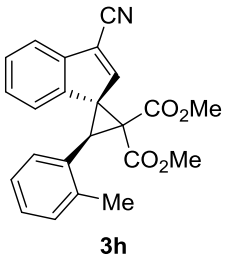

**3f**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(p-tolyl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3f**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +11.1 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.70 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.45 (td, *J* = 7.6, 0.9 Hz, 1H), 7.30 (td, *J* = 7.7, 0.9 Hz, 1H), 7.15–7.09 (m, 3H), 7.04–7.00 (m, 2H), 4.26 (s, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.34 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 166.3, 165.8, 146.9, 140.5, 139.2, 138.1, 129.4, 129.3 (2C), 128.9 (2C), 128.2, 126.9, 121.1, 119.9, 115.4, 114.5, 53.2 (2C), 51.1, 47.0, 41.7, 21.2. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{19}NO_4$ $[M+Na]^+$: 396.1206; found: 396.1208. The enantiomeric excess was determined after hydration of the nitrile to the amide. For the corresponding amide: **UPC$^2$**: IC, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 5.91 min; $t_{minor}$ = 5.43 min.



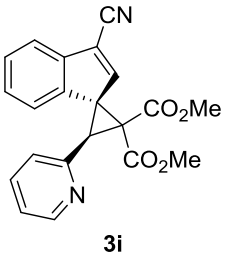
**3g**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(*m*-tolyl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3g**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +41.0 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.71 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.45 (td, *J* = 7.5, 1.0 Hz, 1H), 7.31 (td, *J* = 7.7, 1.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.15–7.09 (m, 2H), 6.97–6.90 (m, 2H), 4.26 (s, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 2.32 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.2, 165.7, 146.7, 140.4, 139.2, 138.3, 132.3, 129.6, 129.0, 128.4, 128.1, 126.9, 126.0, 121.0, 119.8, 115.3, 114.4, 53.2, 53.1, 51.0, 46.8, 41.8, 21.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{19}NO_4$ $[M+H]^+$: 374.1387; found: 374.1394. **UPC$^2$**: IA, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.60 min; $t_{minor}$ = 2.70 min.



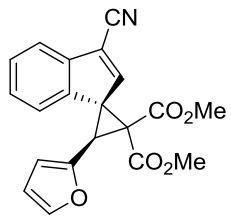
**3h**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(*o*-tolyl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3h**) was isolated as a colourless foam by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +63.6 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.76 (s, 1H), 7.64 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.46 (td, *J* = 7.6, 1.0 Hz, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.24–7.09 (m, 4H), 7.01–6.96 (m, 1H), 4.18 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.20 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.3, 166.0, 146.7, 140.3, 139.1, 138.0, 130.7, 130.3, 128.9, 128.3, 128.2, 127.0, 125.8, 121.1, 119.6, 115.7, 114.4, 53.2, 53.1, 50.2, 47.3, 42.1, 19.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{19}NO_4$ $[M+H]^+$: 374.1387; found: 374.1393. The enantiomeric excess was determined after hydration of the nitrile to the amide. For the corresponding amide: **UPC$^2$**: IC, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 6.01 min; $t_{minor}$ = 5.43 min.



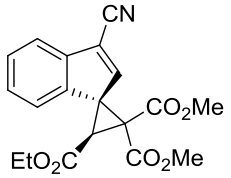
**3i**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(pyridin-2-yl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3i**) was isolated as a colourless foam by FC on silica gel (20:80 EtOAc:pentane). $[\alpha]_D^{25}$ = -348 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.51 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.93 (s, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.42 (td, *J* = 7.3, 1.6 Hz, 1H), 7.34–7.27 (m, 3H), 7.19 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 4.15 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 165.4, 165.3, 153.0, 148.8, 147.5, 139.9, 139.7, 136.5, 128.1, 126.8, 124.7, 122.5, 120.8, 120.6, 114.9, 114.5, 53.4, 53.0, 51.5, 47.8, 42.0. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{16}N_2O_4$ $[M+Na]^+$: 383.1002; found: 383.1007. **UPC$^2$**: IA, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 3.12 min; $t_{minor}$ = 3.51 min.



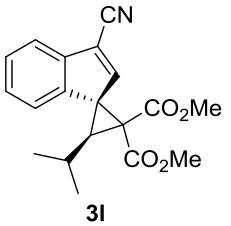
**3j**

Dimethyl (1*R*,3*S*)-3'-cyano-3-(furan-2-yl)spiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3j**) was isolated as a colourless foam by FC on silica gel (10:90 EtOAc:pentane). $[\alpha]_D^{25}$ = -176 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.67 (s, 1H), 7.59 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.35 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.29 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.29 (dt, *J* = 3.3, 0.9 Hz, 1H), 4.09 (s, 1H), 3.78 (s, 3H), 3.70 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 165.2, 165.1, 146.6, 146.2, 142.5, 139.5, 139.4, 128.2, 127.0, 121.0, 120.4, 115.8, 114.2, 110.8, 110.1, 53.4, 53.4, 50.4, 46.7, 34.3. **HRMS** (ESI+) *m*/*z* calcd. for $C_{20}H_{15}NO_5$ $[M+H]^+$: 350.1023; found: 350.1032. The enantiomeric excess was determined after hydration of the nitrile to the amide. For the corresponding amide: **UPC$^2$**: IC, Gradient $CO_2$/*i*PrOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 5.79 min; $t_{minor}$ = 5.26 min.



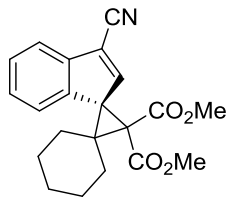
**3k**

3-Ethyl 2,2-dimethyl (1*R*,3*S*)-3'-cyanospiro[cyclopropane-1,1'-indene]-2,2,3-tricarboxylate (**3k**) was isolated as a colourless foam by FC on silica gel (10:90 EtOAc:pentane). $[\alpha]_D^{25}$ = -124 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.61 (s, 1H), 7.58 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30–7.25 (m, 1H), 7.21 (dt, *J* = 7.8, 0.9 Hz, 1H), 4.28–4.14 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.67 (s, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: $^{13}$C 167.0, 164.2, 164.1, 145.5, 139.8, 138.6, 128.7, 127.2, 121.1, 121.0, 116.3, 114.0, 62.3, 53.7, 53.6, 50.0, 45.9, 36.9, 13.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{19}H_{17}NO_6$ $[M+H]^+$: 356.1129; found: 356.1128. The enantiomeric excess was determined after hydration of the nitrile to the amide. For the corresponding amide: **UPC$^2$**: IB, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 3.03 min; $t_{minor}$ = 2.94 min.



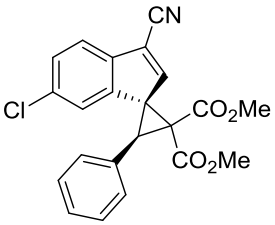
**3l**

Dimethyl (1*R*,3*S*)-3'-cyano-3-isopropylspiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3l**) was isolated as a colourless solid by FC on silica gel (10:90 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +87.0 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.78 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.25 (td, *J* = 7.6, 0.7 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 2.69 (d, *J* = 11.0 Hz, 1H), 2.09–1.96 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.6, 166.3, 145.9, 140.9, 138.9, 127.8, 126.8, 120.9, 119.7, 115.9, 114.5, 53.2, 53.0, 51.0, 47.2, 46.3, 26.5, 22.0, 21.5. **HRMS** (ESI+) *m*/*z* calcd. for $C_{19}H_{19}NO_4$ $[M+H]^+$: 326.1387; found: 326.1392. **UPC$^2$**: IC, Gradient $CO_2$/MeCN, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.54 min; $t_{minor}$ = 2.43 min.



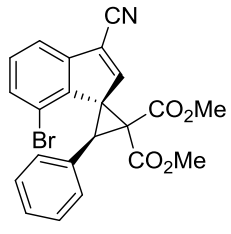

**3m**

Dimethyl (*R*)-3''-cyanodispiro[cyclohexane-1,1'-cyclopropane-2',1''-indene]-3',3'-dicarboxylate (**3m**) was isolated as a pale yellow solid by FC on silica gel (10:90 – 15:85 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +53.8 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.36 (td, *J* = 7.5, 0.9 Hz, 1H), 7.20 (td, *J* = 7.8, 1.2 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.24–2.08 (m, 2H), 1.95–1.84 (m, 2H), 1.71–1.55 (m, 2H), 1.46–1.34 (m, 2H), 1.27–1.13 (m, 1H), 0.94–0.74 (m, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.6, 165.5, 148.4, 139.7, 138.6, 127.3, 126.1, 122.5, 121.1, 114.6, 114.4, 54.3, 53.3, 52.6, 49.8, 45.7, 31.6, 28.9, 25.5, 25.3, 25.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{21}H_{21}NO_4$ $[M+H]^+$: 352.1543; found: 352.1542. **UPC$^2$**: IA, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.67 min; $t_{minor}$ = 2.76 min.



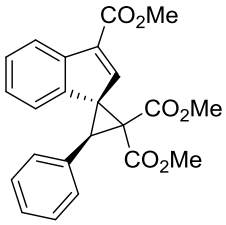

**3n**

Dimethyl (1*R*,3*S*)-6'-chloro-3'-cyano-3-phenylspiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3n**) was isolated as a colourless foam by FC on silica gel (10:90 – 20:80 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +36.2 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.67 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.35–7.30 (m, 3H), 7.15–7.09 (m, 3H), 4.28 (s, 1H), 3.73 (s, 3H) 3.72 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 166.0, 165.4, 146.9, 142.2, 137.7, 133.4, 132.1, 129.0 (2C), 128.7 (2C), 128.4 (2C), 121.9, 120.7, 114.8, 114.0, 53.5, 53.4, 51.2, 46.6, 42.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{16}ClNO_4$ $[M+Na]^+$: 416.0660; found: 416.0664. **UPC$^2$**: IA, $CO_2$/MeOH 2% isocratic, 3.0 mL·min$^{-1}$; $t_{major}$ = 3.25 min; $t_{minor}$ = 3.68 min.



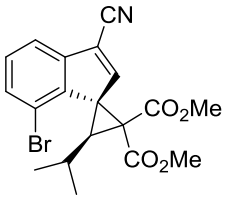

**3o**

Dimethyl (1*S*,3*S*)-7'-bromo-3'-cyano-3-phenylspiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3o**) was isolated as a colourless foam by FC on silica gel (15:85 – 20:80 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +316 (*c* 0.5, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.63–7.58 (m, 2H), 7.47 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.38–7.32 (m, 3H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.20–7.15 (m, 2H), 5.53 (s, 1H), 3.83 (s, 3H), 3.70 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.2, 166.1, 147.6, 142.6, 136.8, 132.6, 132.4, 129.4, 129.0 (2C), 128.4 (2C), 127.9, 120.5, 117.7, 114.2, 113.7, 53.7, 53.4, 49.5, 47.4, 38.1. **HRMS** (ESI+) *m*/*z* calcd. for $C_{22}H_{16}BrNO_4$ $[M+H]^+$: 438.0335/440.03115; found: 438.0343/440.03125. **UPC$^2$**: ID, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.87 min; $t_{minor}$ = 2.75 min.



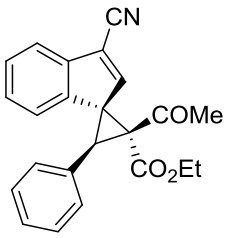

**3p**

Trimethyl (1*R*,3*S*)-3-phenylspiro[cyclopropane-1,1'-indene]-2,2,3'-tricarboxylate (**3p**) was isolated as a colourless foam by FC on silica gel (10:90 – 20:80 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +58.8 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.14 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.83 (s, 1H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.35–7.28 (m, 3H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.21–7.17 (m, 2H), 7.08 (dt, *J* = 7.8, 0.9 Hz, 1H), 4.26 (s, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 166.6, 166.0, 164.0, 143.3, 141.7, 139.9, 134.6, 133.0, 129.2 (2C), 128.4 (2C), 127.9, 127.7, 125.7, 123.0, 119.3, 53.1, 53.0, 51.6, 50.4, 46.1, 41.4. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{20}O_6$ $[M+H]^+$: 393.1333; found: 393.1339. **UPC$^2$**: IA, Gradient $CO_2$/MeCN, 3.0 mL·min$^{-1}$; $t_{major}$ = 3.01 min; $t_{minor}$ = 3.10 min.




**3q**

Dimethyl (1*S*,3*S*)-7'-bromo-3'-cyano-3-isopropylspiro[cyclopropane-1,1'-indene]-2,2-dicarboxylate (**3q**) was isolated as white crystals by FC on silica gel (10:90 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +331 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.73 (s, 1H), 7.54 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.41 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.76 (d, *J* = 8.1 Hz, 6H), 2.68–2.55 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 167.6, 166.4, 147.0, 142.5, 137.5, 132.4, 129.0, 120.5, 117.7, 114.8, 113.9, 53.7, 53.5, 50.1, 48.0, 43.0, 25.1, 22.1, 21.7. **HRMS** (ESI+) *m*/*z* calcd. for $C_{19}H_{18}BrNO_4$ $[M+H]^+$: 404.0492/406.0472; found: 404.0493/406.0475. **UPC$^2$**: IC, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 2.58 min; $t_{minor}$ = 2.48 min.

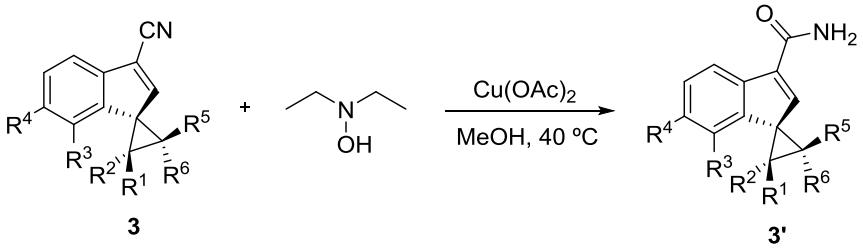



**3r**

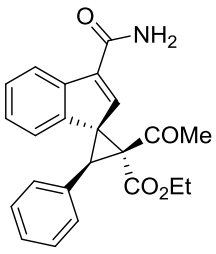
Ethyl (1*R*,2*R*,3*S*)-2-acetyl-3'-cyano-3-phenylspiro[cyclopropane-1,1'-indene]-2-carboxylate (**3r**) was isolated as a colourless foam by FC on silica gel (10:90 – 20:80 $Et_2O$:pentane). $[\alpha]_D^{25}$ = +84.0 (*c* 1.0, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.82 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.44 (td, *J* = 7.5, 0.6 Hz, 1H), 7.34–7.28 (m, 4H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.10–7.09 (m, 2H), 4.36 (s, 1H), 4.25 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.37 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 197.1, 167.0, 146.5, 140.3, 139.1, 132.2, 129.2 (2C), 128.7 (2C), 128.2, 128.1 126.7, 121.0, 120.2, 115.2, 114.6, 62.7, 58.2, 48.5, 44.0, 30.7, 13.9. **HRMS** (ESI+) *m*/*z* calcd. for $C_{23}H_{19}NO_3$ $[M+H]^+$: 358.1438; found: 358.1444. The enantiomeric excess was determined after hydration of the nitrile to the amide. For the corresponding amide: **UPC$^2$**: IB, Gradient $CO_2$/MeOH, 3.0 mL·min$^{-1}$; $t_{major}$ = 3.43 min; $t_{minor}$ = 3.34 min.

## 6. Preparation of cyclopropane spiroindene amides 3'

The corresponding amides of **3f**, **3h**, **3j**, **3k** and **3r** were prepared with inspiration from a previously described procedure.[8]




In a 4 mL vial containing a stirring bar, the appropriate nitrile **3** (0.025 mmol, 1 eq) was dissolved in MeOH (0.1 mL). A spatula tip of copper acetate was added, followed by hydroxylamine (6.4 µL, 0.0625 mmol, 2.5 eq). The reaction mixture was heated to 40 °C and stirred until completion. The reaction mixture was diluted with 10 mL water and 10 mL $Et_2O$. The phases were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic phases were concentrated and purified by FC on silica gel to afford cyclopropane spiroindene amide **3'**. **3r'** has been fully characterised as a representative example. **3f'**, **3h'** and **3j'** were submitted to UPC[2] analysis directly from the crude reaction mixture.



**3r'**

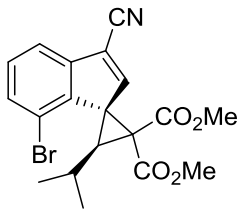
Ethyl (1*R*,2*R*,3*S*)-2-acetyl-3'-carbamoyl-3-phenylspiro[cyclopropane-1,1'-indene]-2-carboxylate (**3r'**) was isolated as a colourless foam by FC on silica gel (30:70 EtOAc:pentane). $[\alpha]_D^{25}$ = +136.4 (*c* 0.5, $CH_2Cl_2$). **$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.38 (td, *J* = 7.6, 0.9 Hz, 1H), 7.32–7.27 (m, 3H), 7.22 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13–7.09 (m, 3H), 6.08 (bs, 1H), 5.60 (bs, 1H), 4.32 (s, 1H), 4.24 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.38 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ 198.3, 167.5, 166.3, 141.7, 140.3, 137.4, 136.5, 132.9, 129.4 (2C), 128.5 (2C), 127.8, 127.8, 125.7, 123.2, 119.5, 62.5, 57.0, 48.1, 43.3, 31.0, 13.9. **HRMS** (ESI+) *m/z* calcd. for $C_{23}H_{21}NNaO_4$ $[M+Na]^+$: 398.1363; found: 398.1371.

[8] P. Marcé, J. Lynch, A. J. Blacker and J. M. J. Williams, *Chem. Commun*., 2016, **52**, 1436-1438.

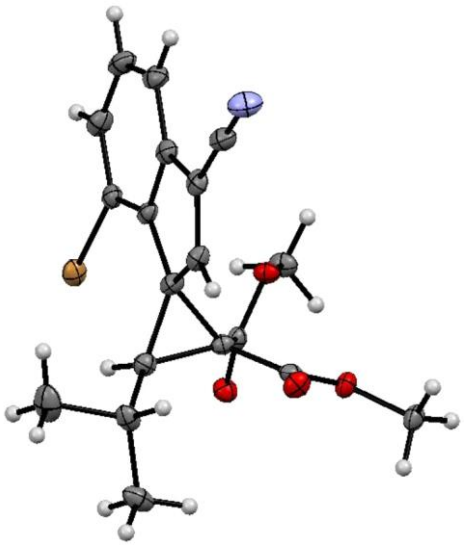
## 7. Crystallographic data for compound 3q

CCDC number: 1498908

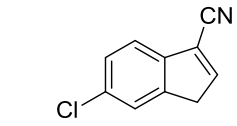
| Item | Value |
|---|---|
| Molecular formula | $C_{19}H_{18}BrNO_4$ |
| Formula weight | 404.26 |
| Crystal system | trigonal |
| Space Group | P 3 |
| a (Å) | 15.6261 |
| b (Å) | 15.6261 |
| c (Å) | 6.58142 |
| α (°) | 90 |
| β (°) | 90 |
| γ (°) | 120 |
| Volume ($Å^3$) | 1391.72 |
| Z | 3 |
| T (K) | 100 |
| ρ (g $cm^{-1}$) | 1.447 |
| λ (Å) | 0.71073 |
| μ ($mm^{-1}$) | 2.237 |
| # measured refl | 28798 |
| # unique refl | 4732 |
| $R_{int}$ | 0.0463 |
| # parameters | 230 |
| $R(F^2)$, all refl | 0.0374 |
| $R_w(F^2)$, all refl | 0.0517 |
| Goodness of fit | 1.05 |




**3q**

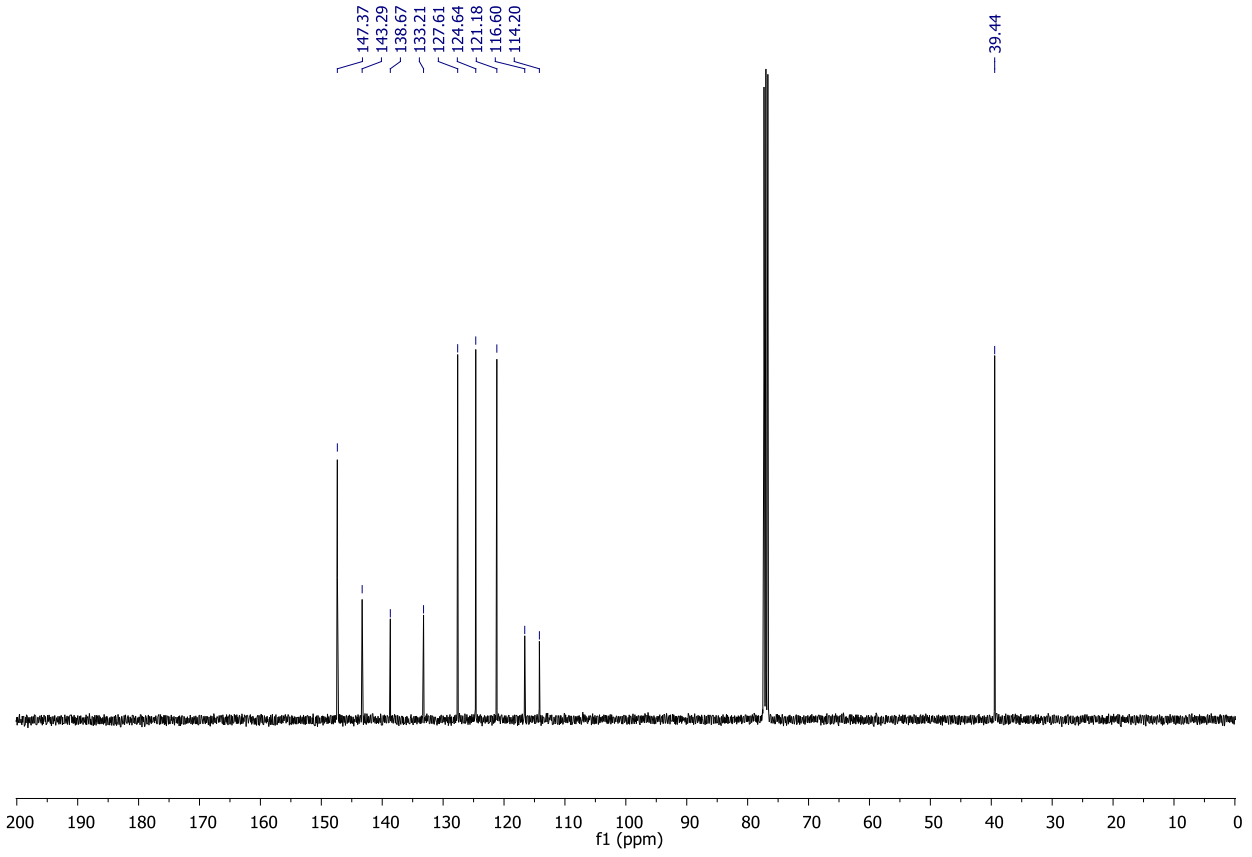


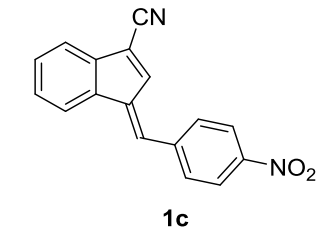
## 8. NMR spectra





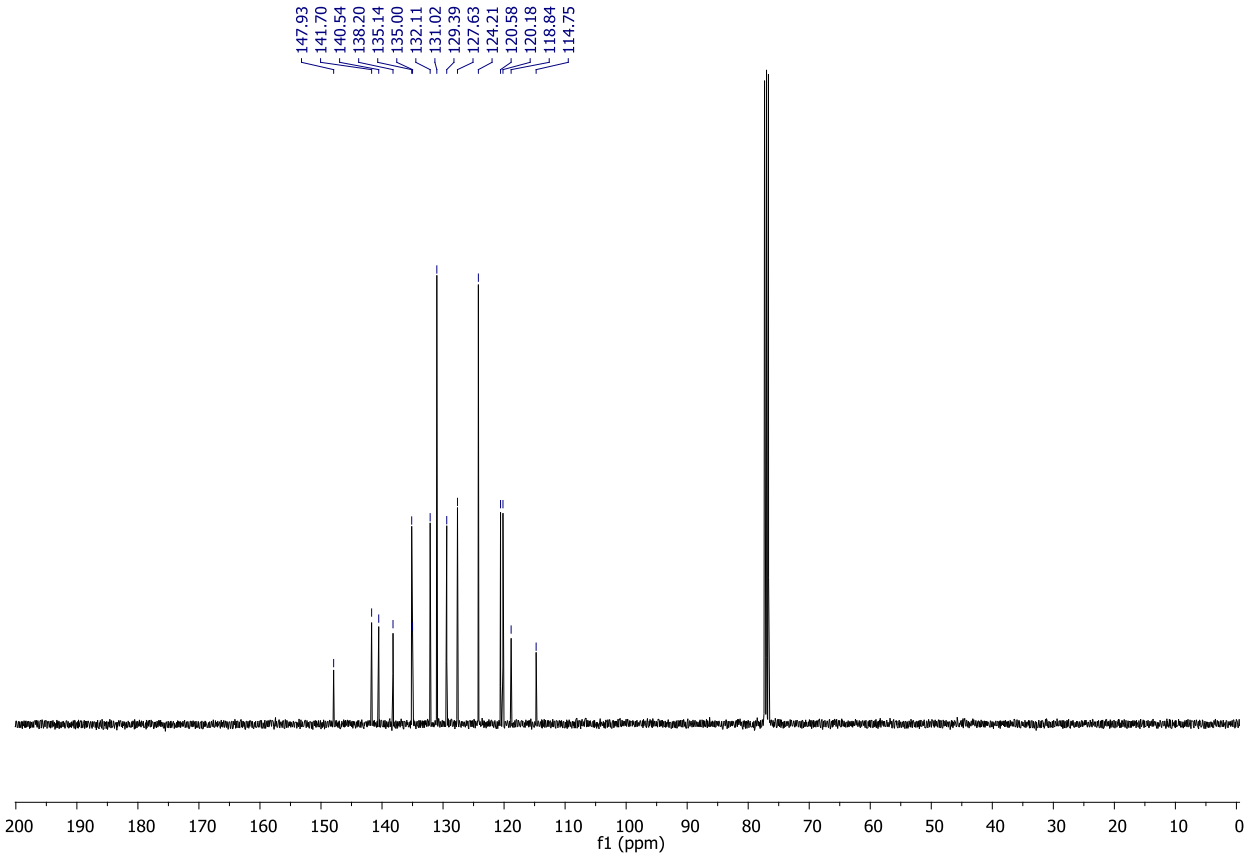


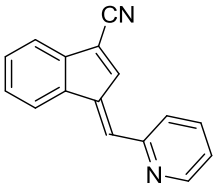



CN
NO2

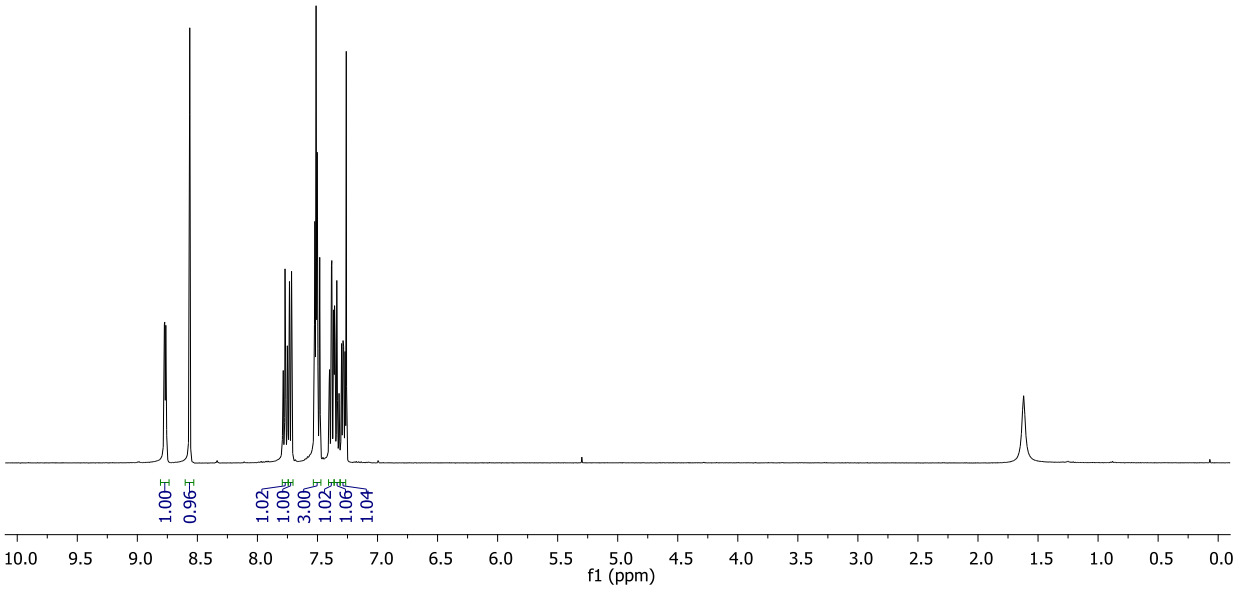
**1c**

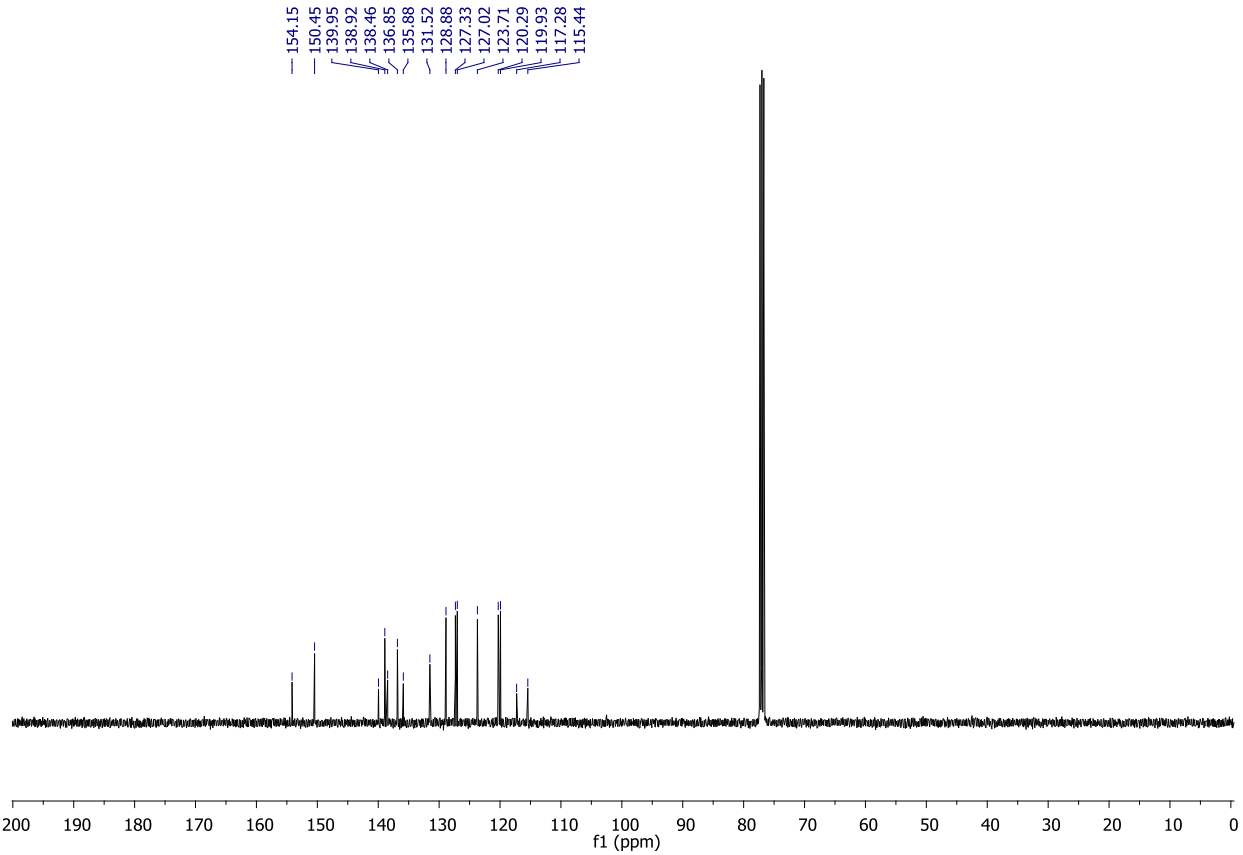

2.00
4.17
1.11
3.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

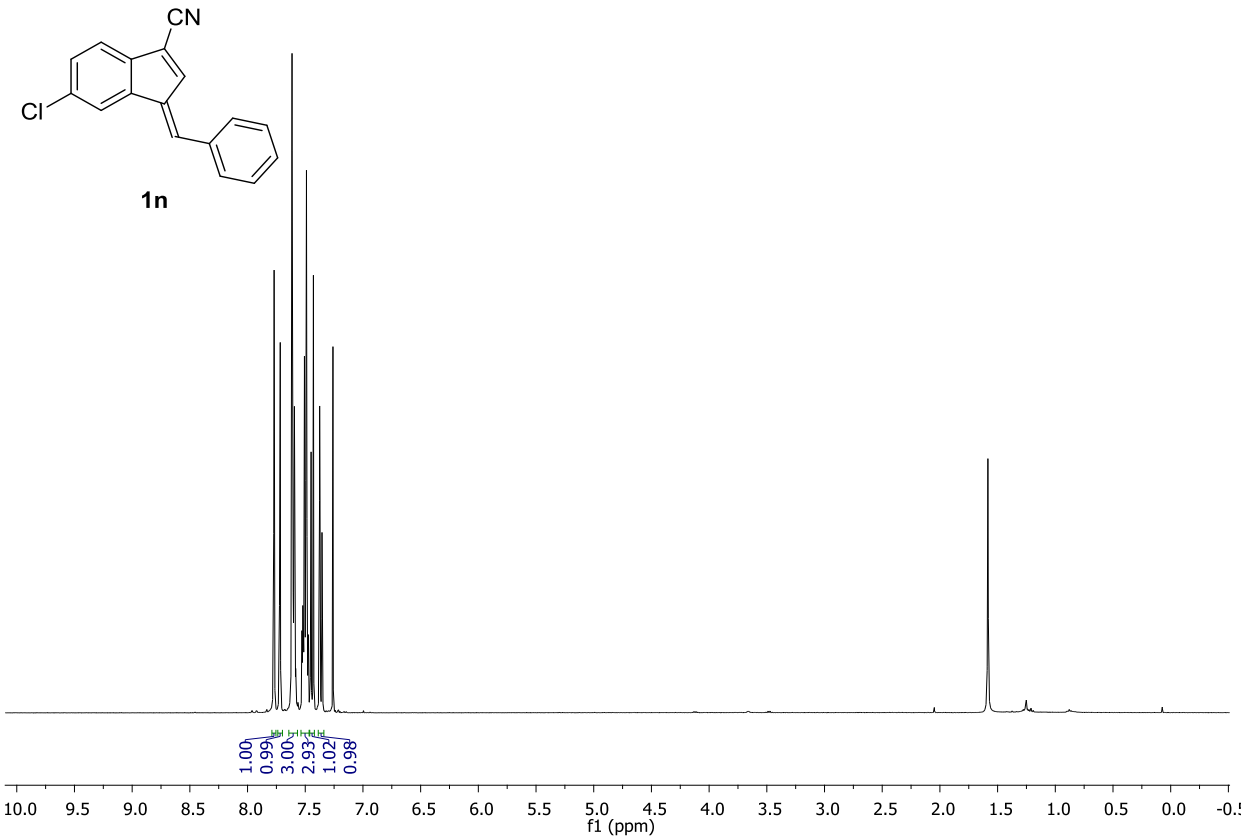

147.93
141.70
140.54
138.20
135.14
135.00
132.11
131.02
129.39
127.63
124.21
120.58
120.18
118.84
114.75
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

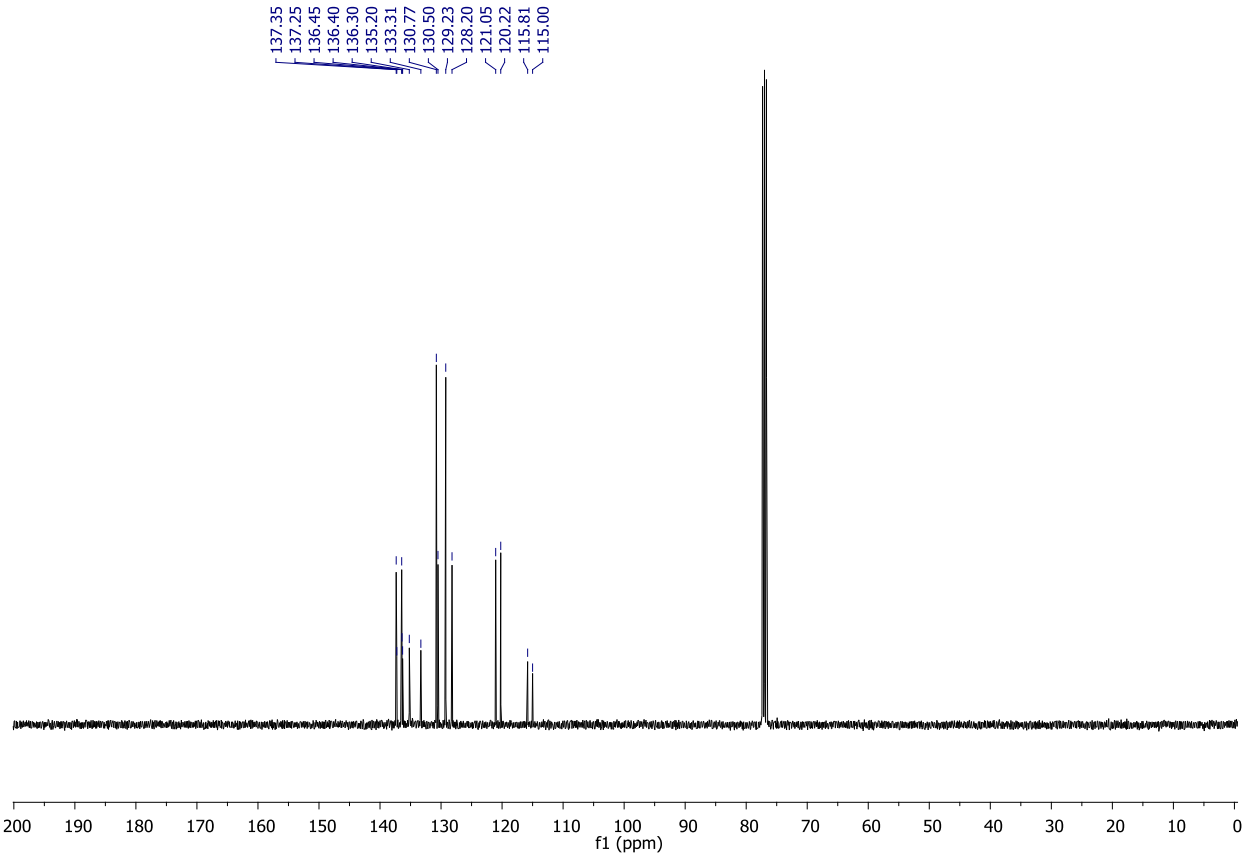

CN
N

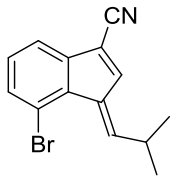
**1i**


1.00
0.96
1.02
1.00
3.00
1.02
1.06
1.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


154.15
150.45
139.95
138.92
138.46
136.85
135.88
131.52
128.88
127.33
127.02
123.71
120.29
119.93
117.28
115.44
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

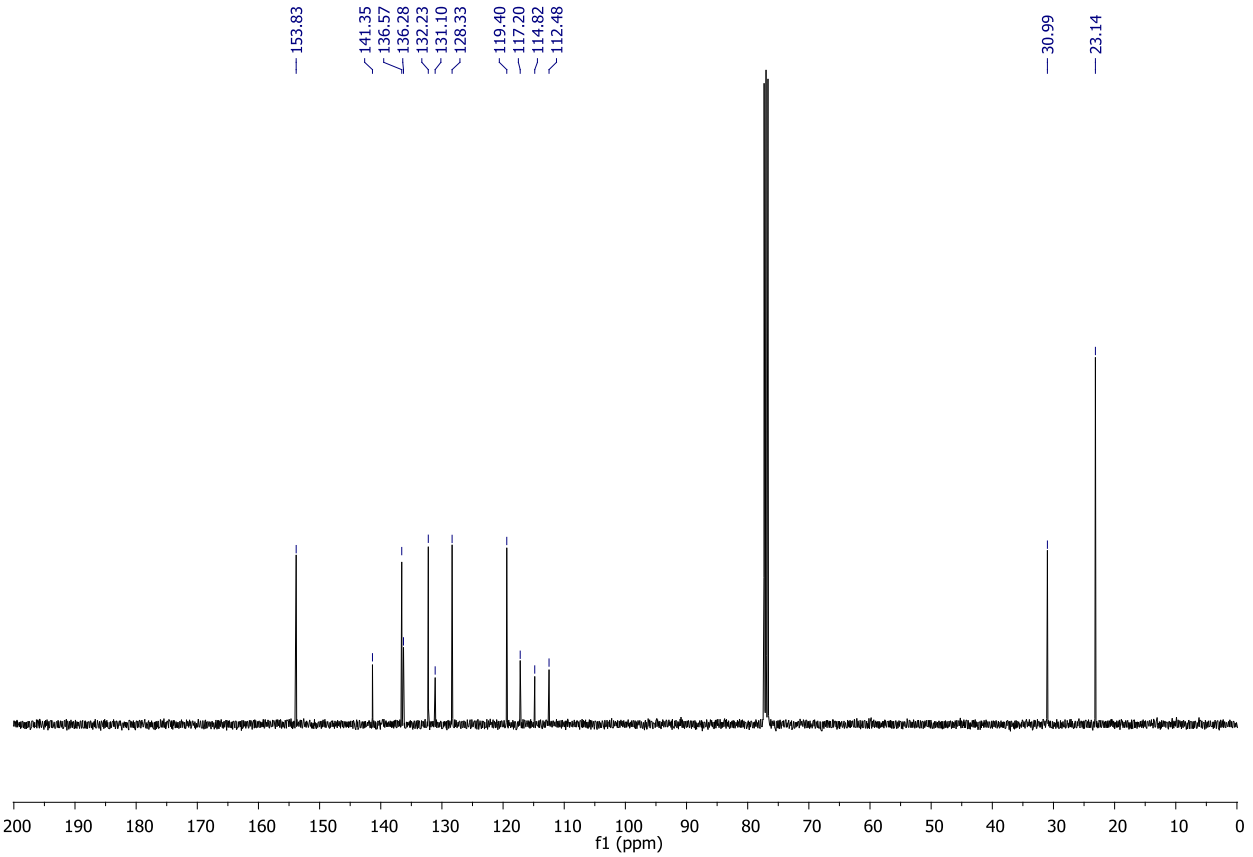

CN
Cl
1n
1.00
0.99
3.00
2.93
1.02
0.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

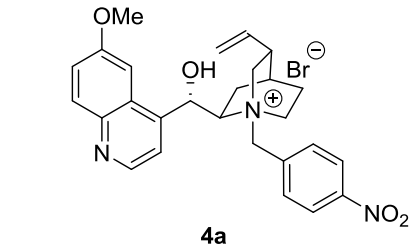

137.35
137.25
136.45
136.40
136.30
135.20
133.31
130.77
130.50
129.23
128.20
121.05
120.22
115.81
115.00
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
Br

**1q**

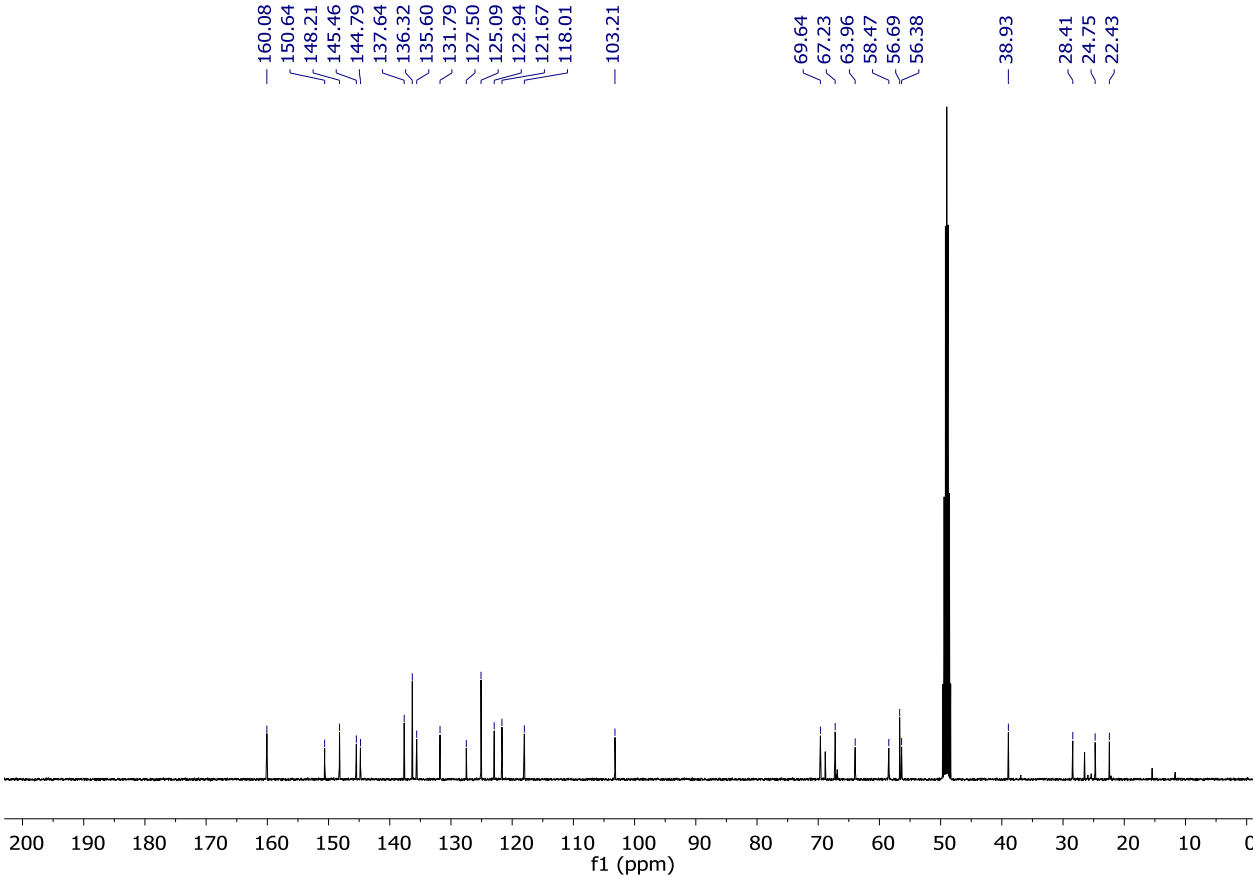

1.00
1.01
1.97
1.01
1.08
6.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

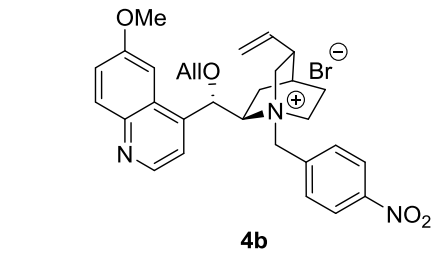

153.83
141.35
136.57
136.28
132.23
131.10
128.33
119.40
117.20
114.82
112.48
30.99
23.14
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
OH
Br
N
N
NO2

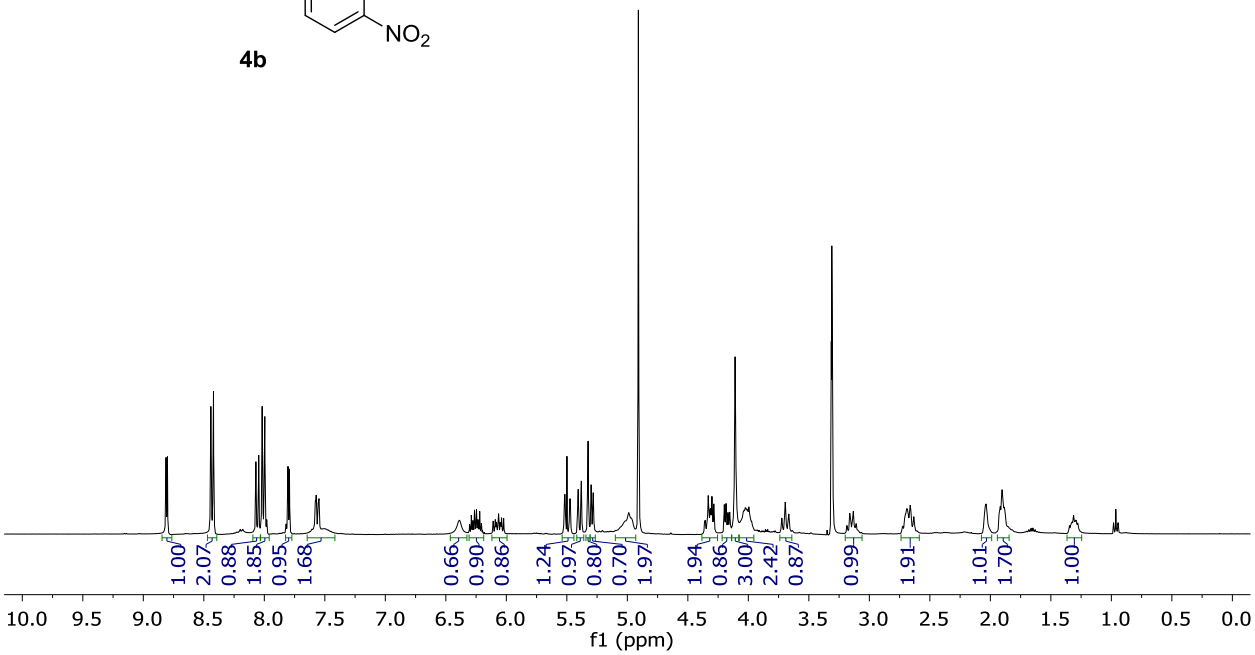
**4a**

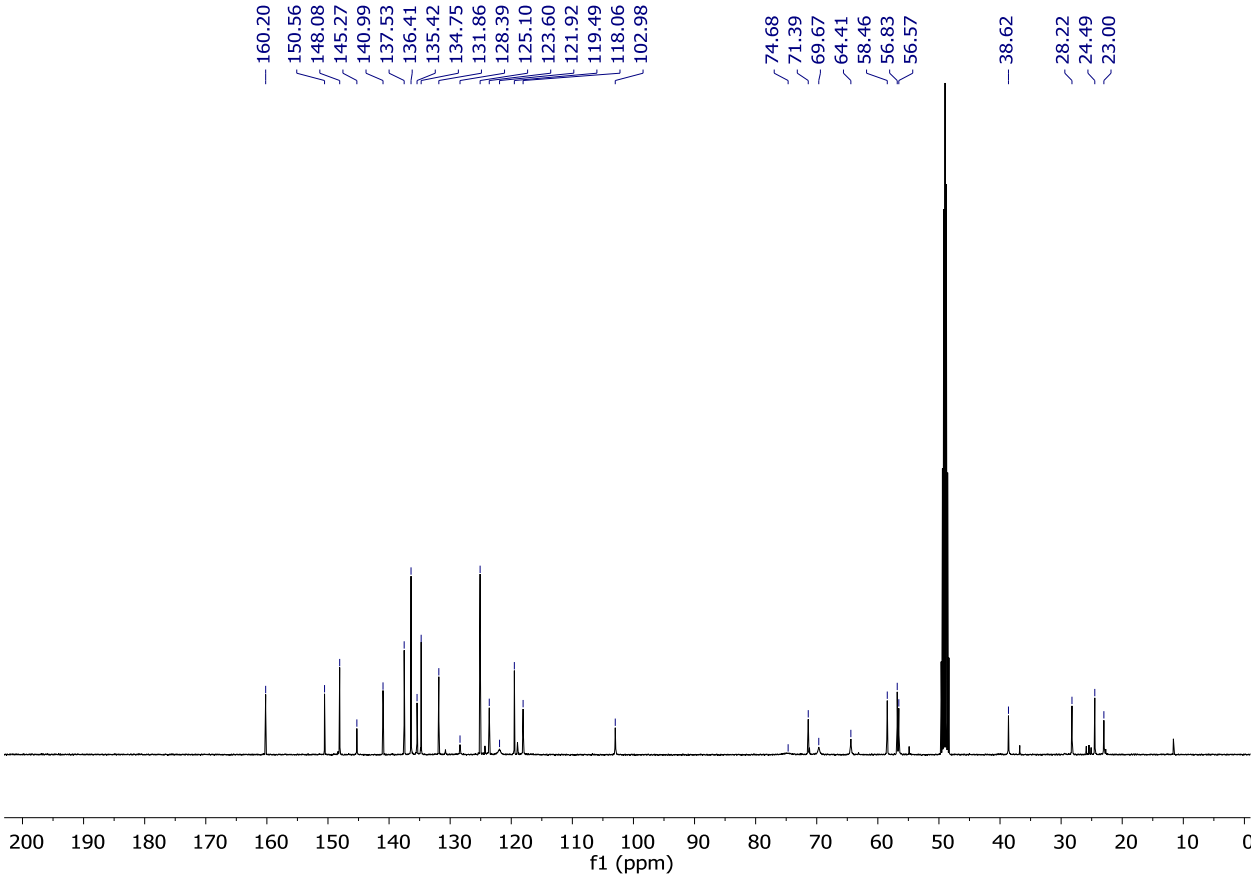

1.00
1.99
2.98
1.00
0.82
0.77
1.00
0.92
0.75
0.68
0.70
0.82
0.90
2.98
1.88
0.91
0.95
0.87
0.93
0.92
2.31
1.54
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

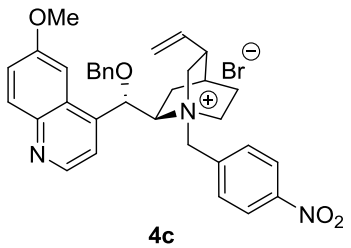

160.08
150.64
148.21
145.46
144.79
137.64
136.32
135.60
131.79
127.50
125.09
122.94
121.67
118.01
103.21
69.64
67.23
63.96
58.47
56.69
56.38
38.93
28.41
24.75
22.43
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
AllO
Br
N
N
NO2

**4b**

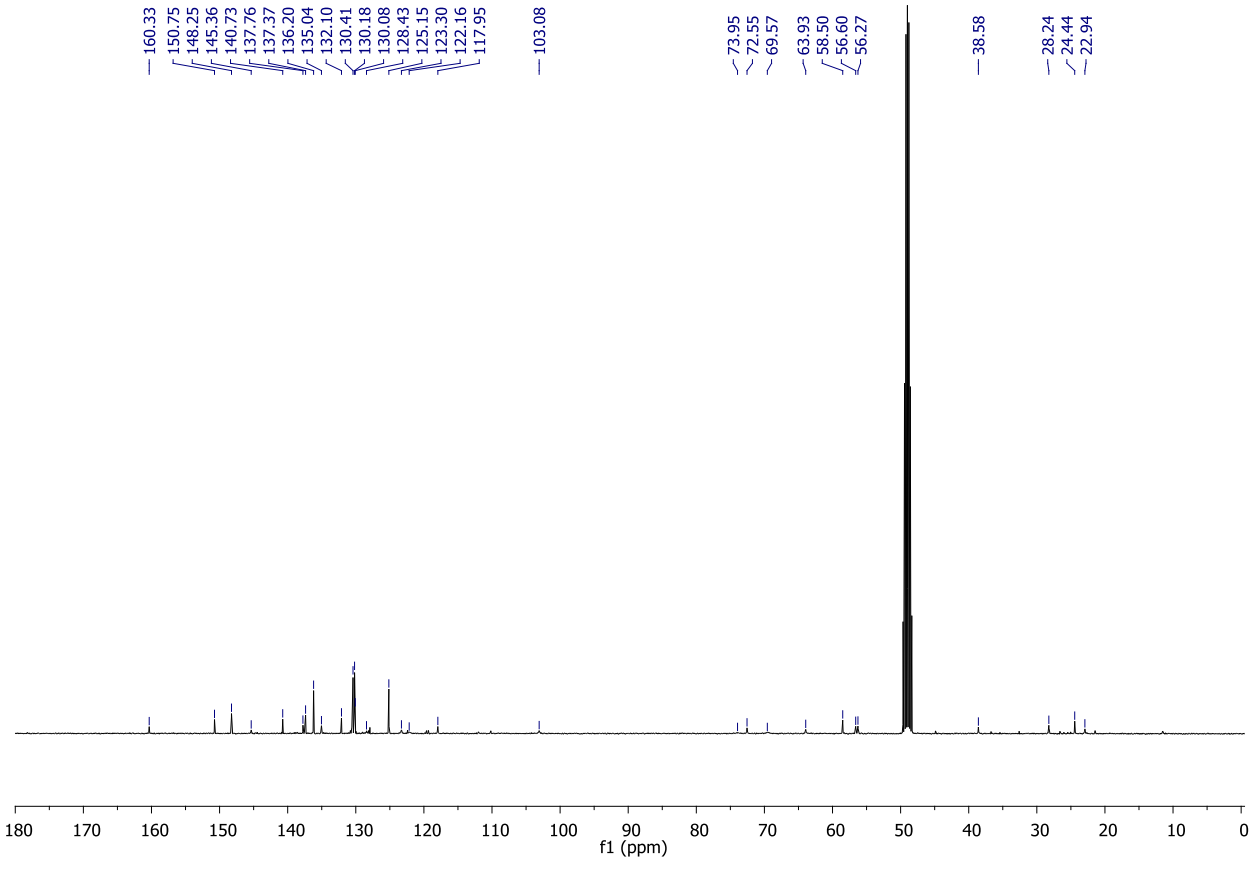

1.00
2.07
0.88
1.85
0.95
1.68
0.66
0.90
0.86
1.24
0.97
0.80
0.70
1.97
1.94
0.86
3.00
2.42
0.87
0.99
1.91
1.01
1.70
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

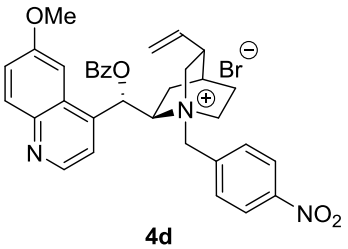

160.20
150.56
148.08
145.27
140.99
137.53
136.41
135.42
134.75
131.86
128.39
125.10
123.60
121.92
119.49
118.06
102.98
74.68
71.39
69.67
64.41
58.46
56.83
56.57
38.62
28.22
24.49
23.00
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
BnO
Br
N
N
NO2

**4c**

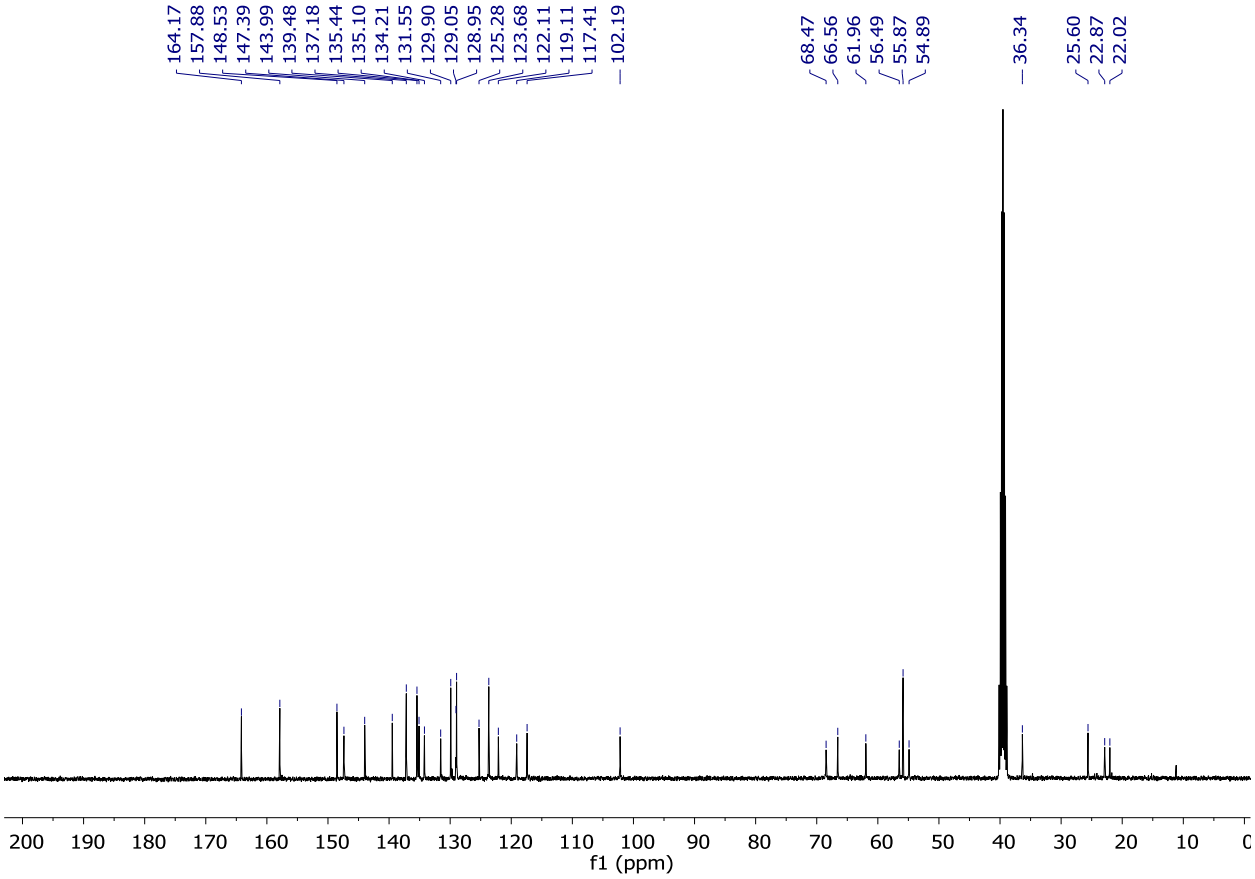

1.00
2.03
0.94
3.01
7.82
1.07
0.96
1.88
3.34
1.14
5.23
0.82
1.09
1.91
1.05
1.76
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

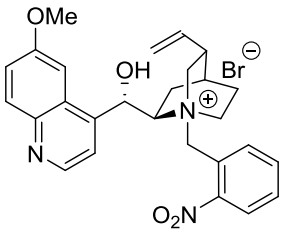

160.33
150.75
148.25
145.36
140.73
137.76
137.37
136.20
135.04
132.10
130.41
130.18
130.08
128.43
125.15
123.30
122.16
117.95
103.08
73.95
72.55
69.57
63.93
58.50
56.60
56.27
38.58
28.24
24.44
22.94
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
BzO
Br
N
N
NO2

**4d**

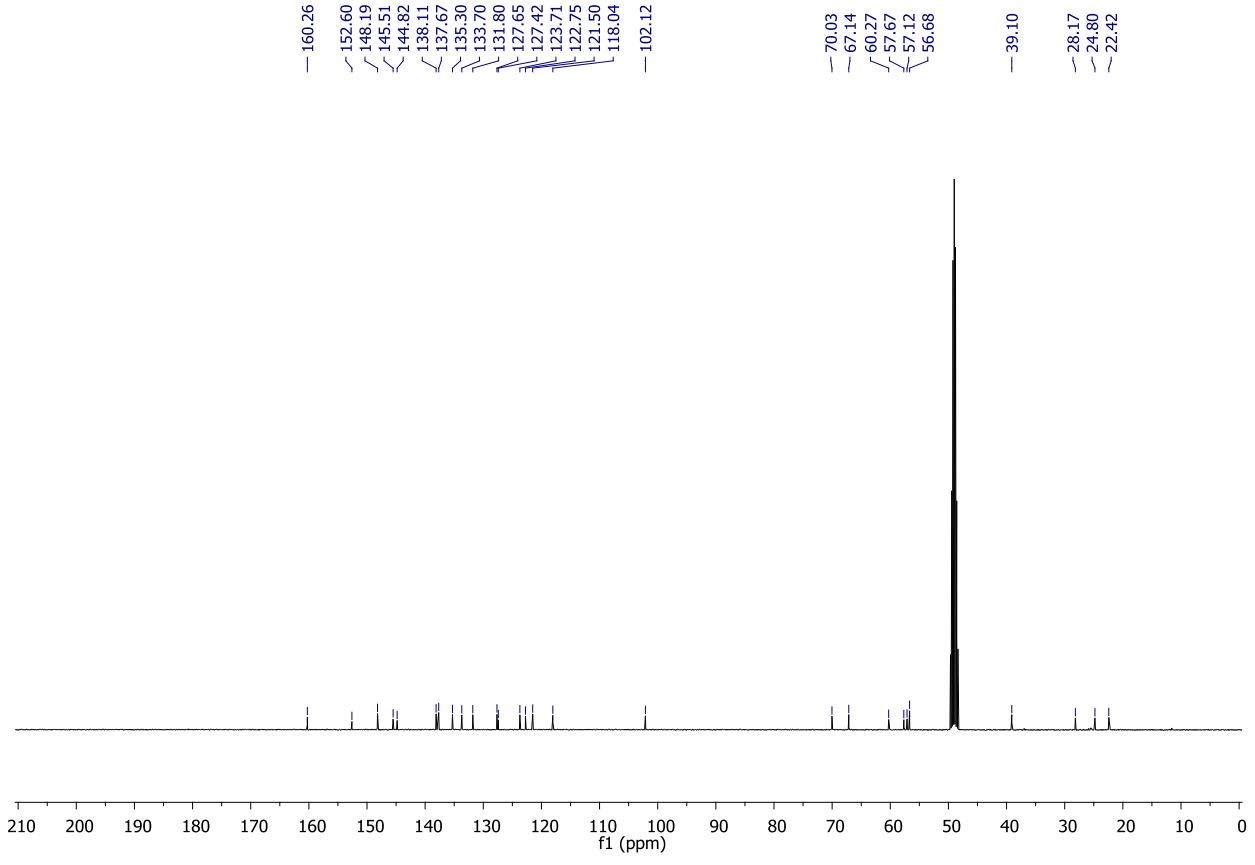

1.00
2.04
2.00
3.03
1.03
2.89
1.04
1.00
1.02
0.94
0.94
1.00
1.04
1.06
1.07
4.05
1.05
1.11
3.16
0.97
3.39
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

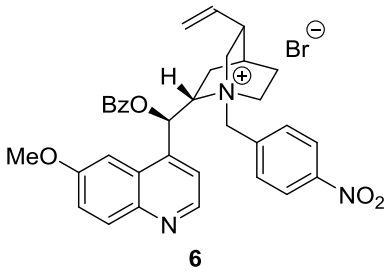

164.17
157.88
148.53
147.39
143.99
139.48
137.18
135.44
135.10
134.21
131.55
129.90
129.05
128.95
125.28
123.68
122.11
119.11
117.41
102.19
68.47
66.56
61.96
56.49
55.87
54.89
36.34
25.60
22.87
22.02
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
OH
Br
N
N
O2N

**5**

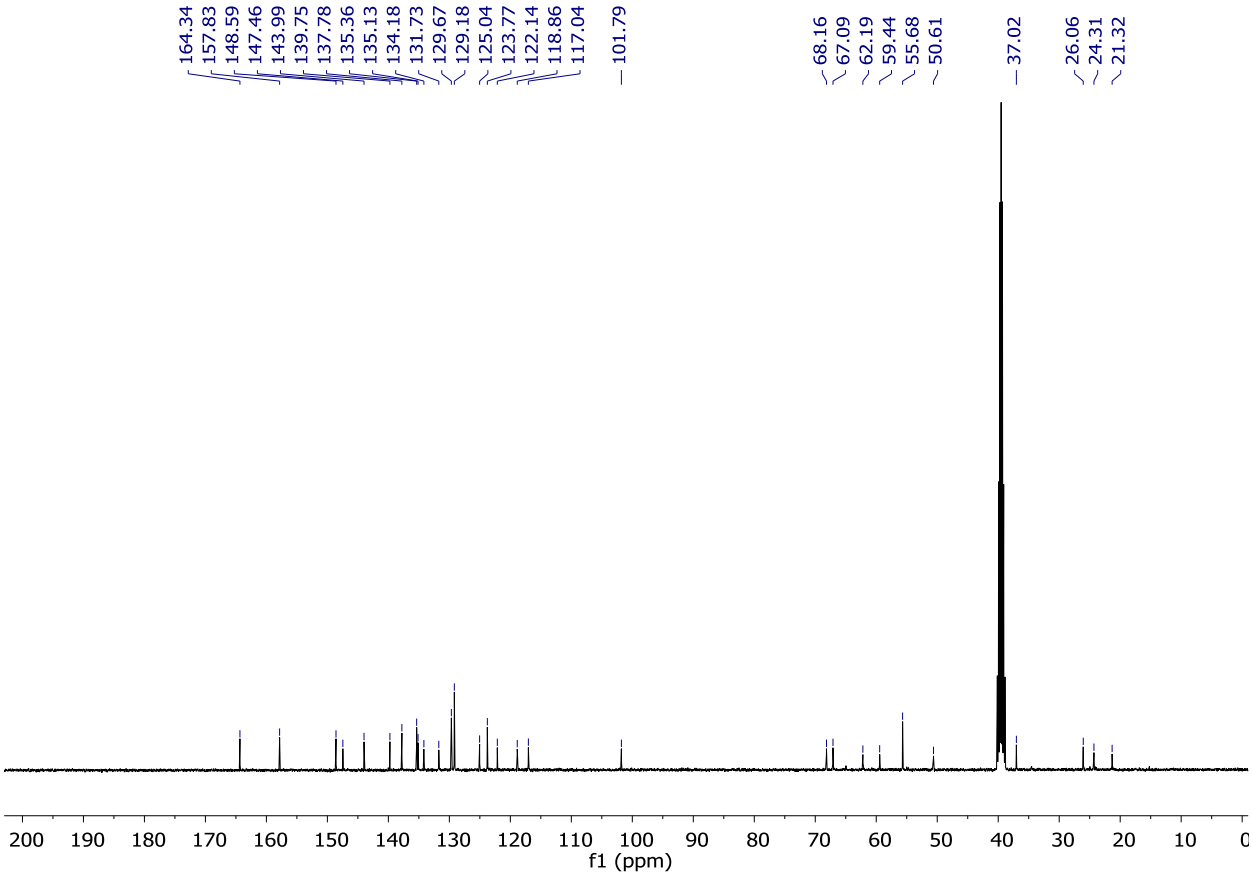

1.00
0.99
1.98
3.03
0.98
1.05
1.03
0.97
2.08
1.91
0.92
2.98
0.67
0.89
0.95
0.96
0.94
0.94
3.17
0.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

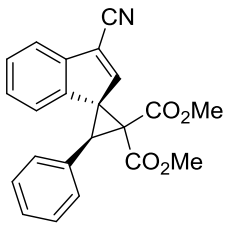

160.26
152.60
148.19
145.51
144.82
138.11
137.67
135.30
133.70
131.80
127.65
127.42
123.71
122.75
121.50
118.04
102.12
70.03
67.14
60.27
57.67
57.12
56.68
39.10
28.17
24.80
22.42
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
H
N
BzO
MeO
NO2
N

**6**

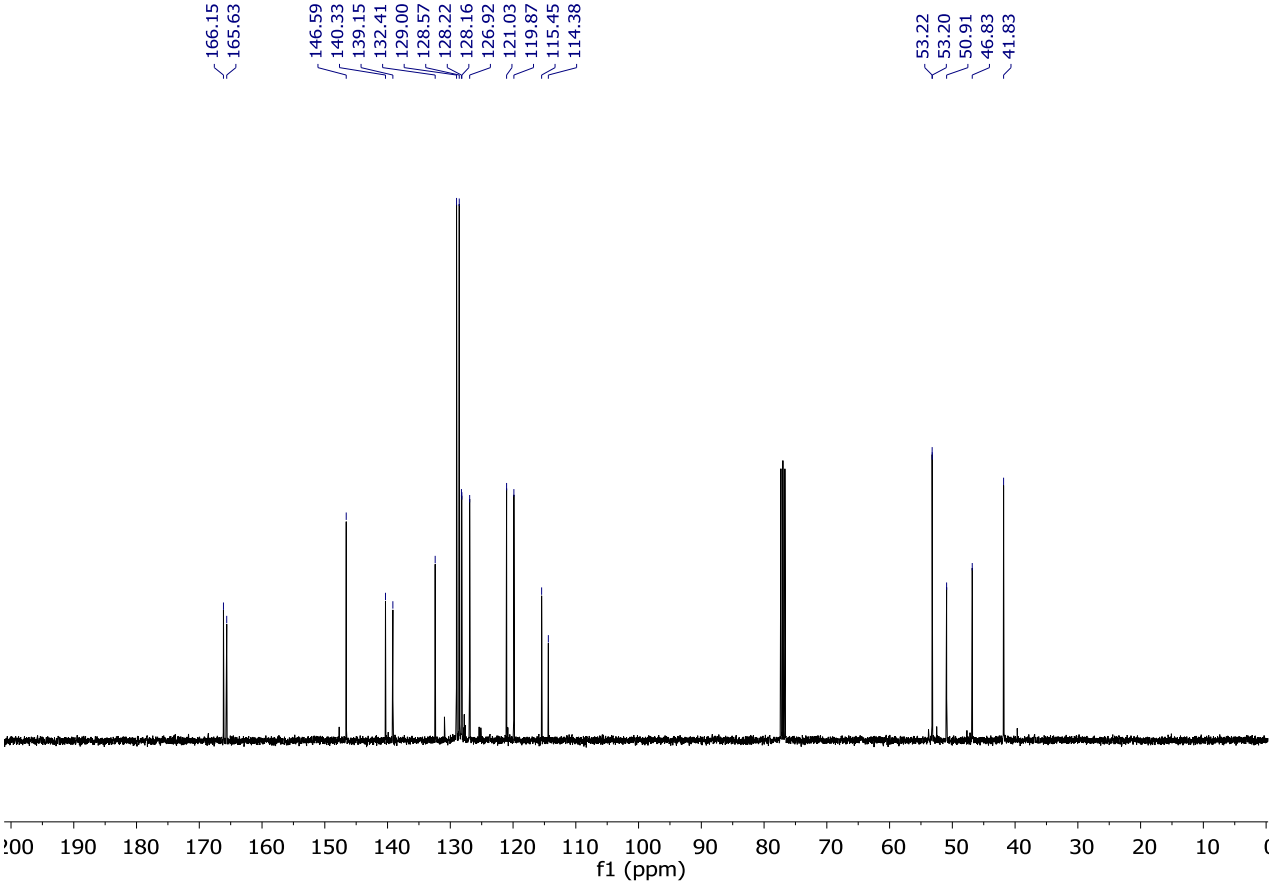

1.04
2.14
2.09
1.04
2.09
2.07
4.11
1.03
0.97
0.98
2.06
1.01
3.00
0.84
3.22
2.03
1.03
1.07
1.98
0.71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

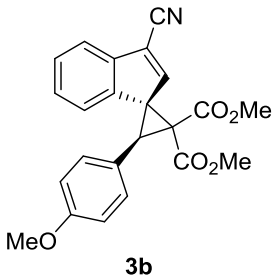

164.34
157.83
148.59
147.46
143.99
139.75
137.78
135.36
135.13
134.18
131.73
129.67
129.18
125.04
123.77
122.14
118.86
117.04
101.79
68.16
67.09
62.19
59.44
55.68
50.61
37.02
26.06
24.31
21.32
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me

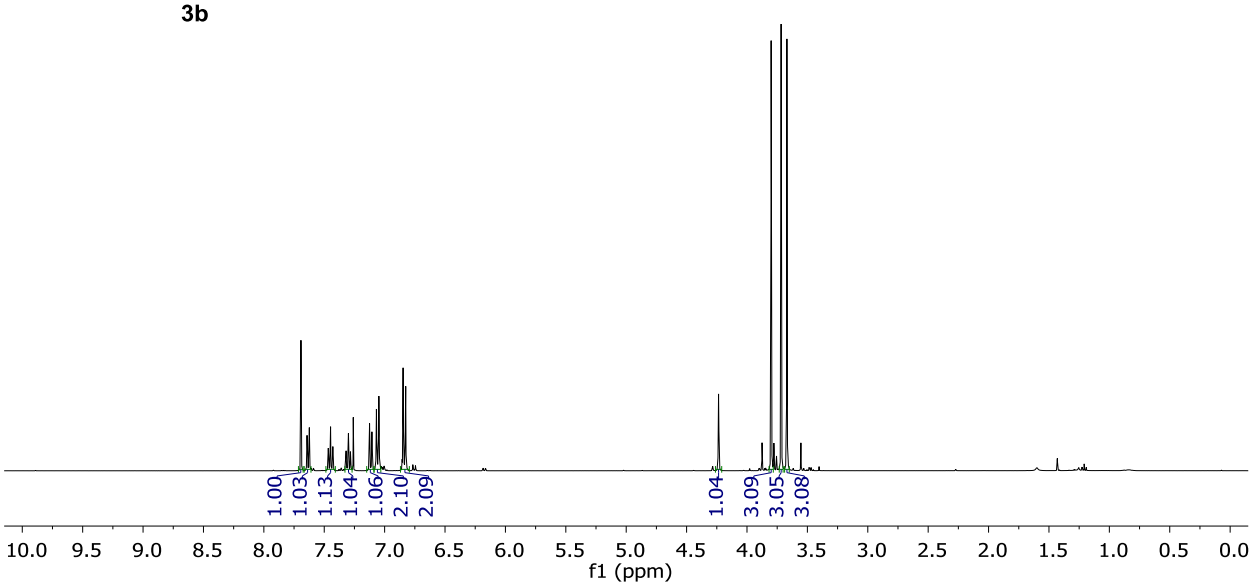
**3a**

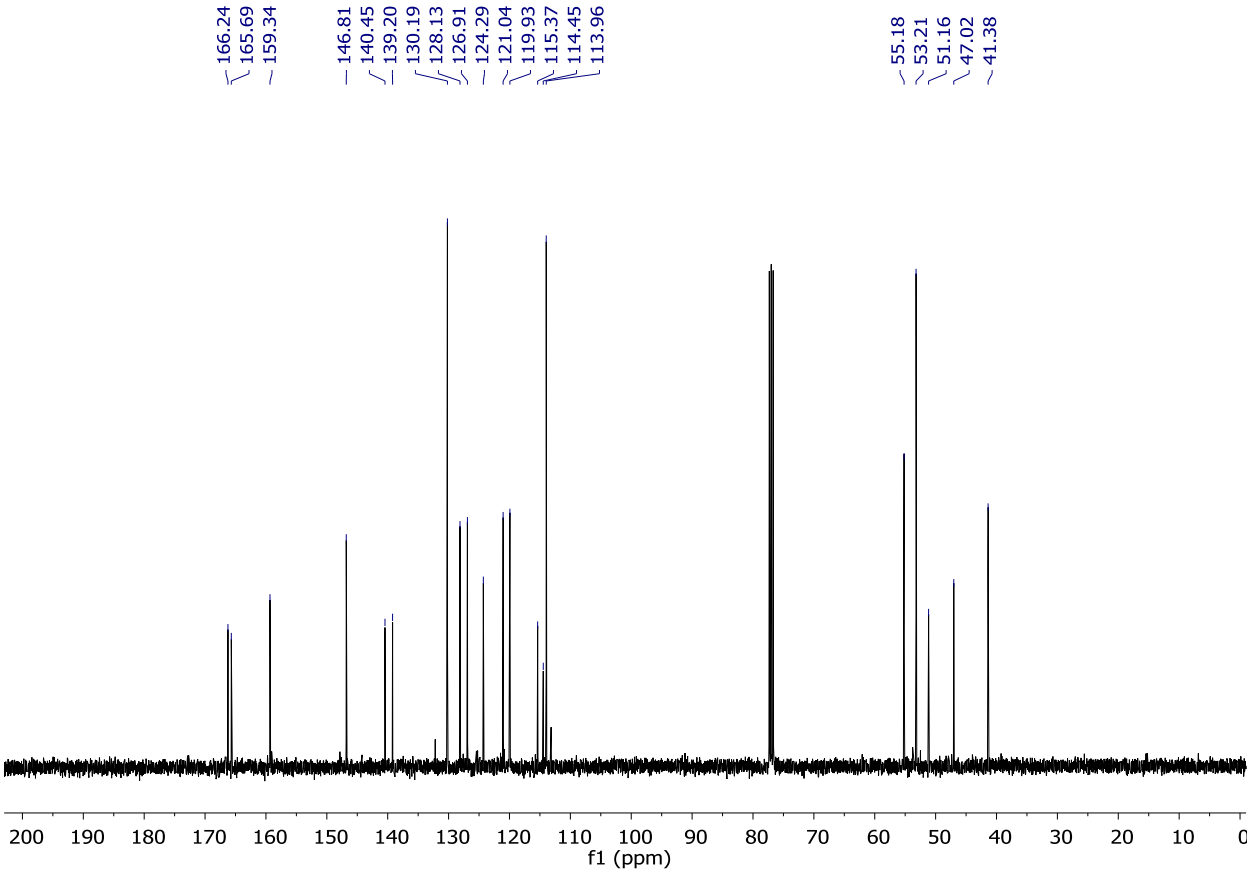

0.91
0.95
0.91
3.99
2.97
1.00
2.91
2.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

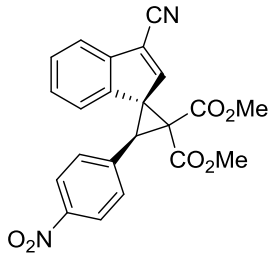

166.15
165.63
146.59
140.33
139.15
132.41
129.00
128.57
128.22
128.16
126.92
121.03
119.87
115.45
114.38
53.22
53.20
50.91
46.83
41.83
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
MeO

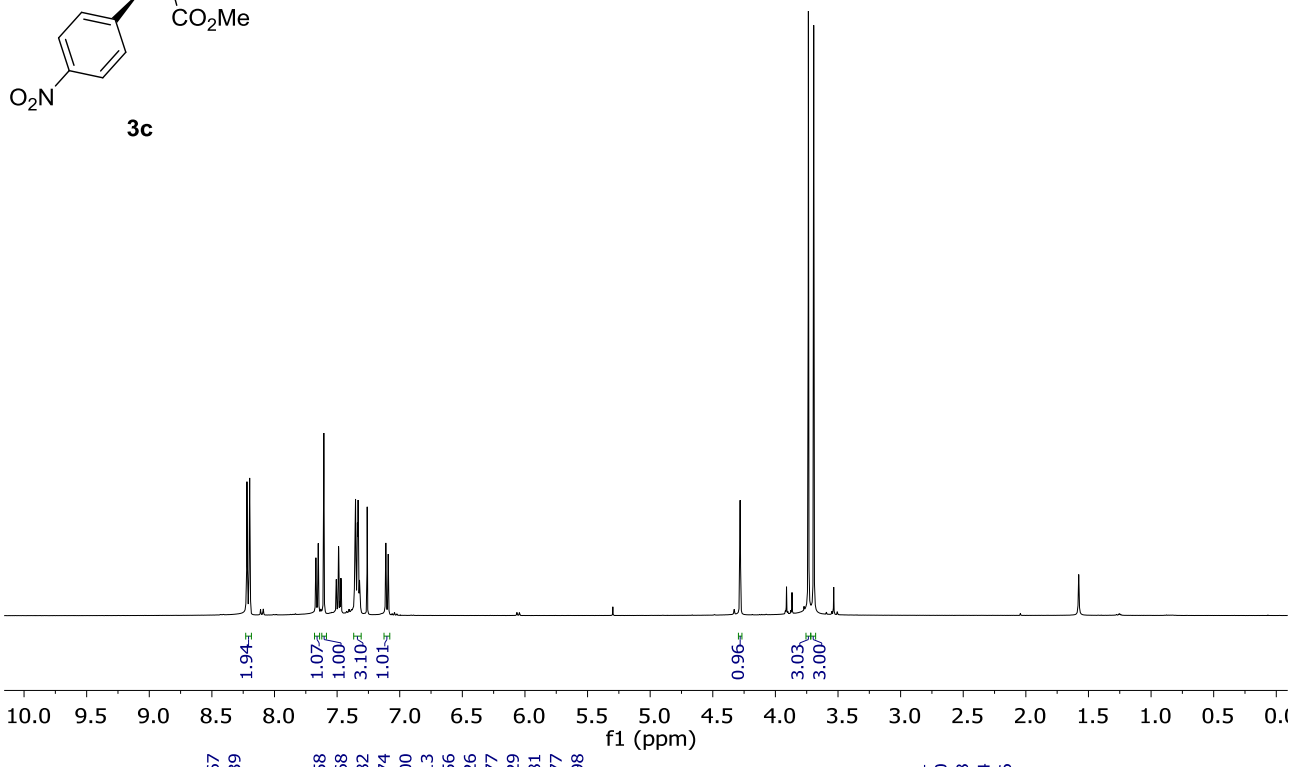
**3b**

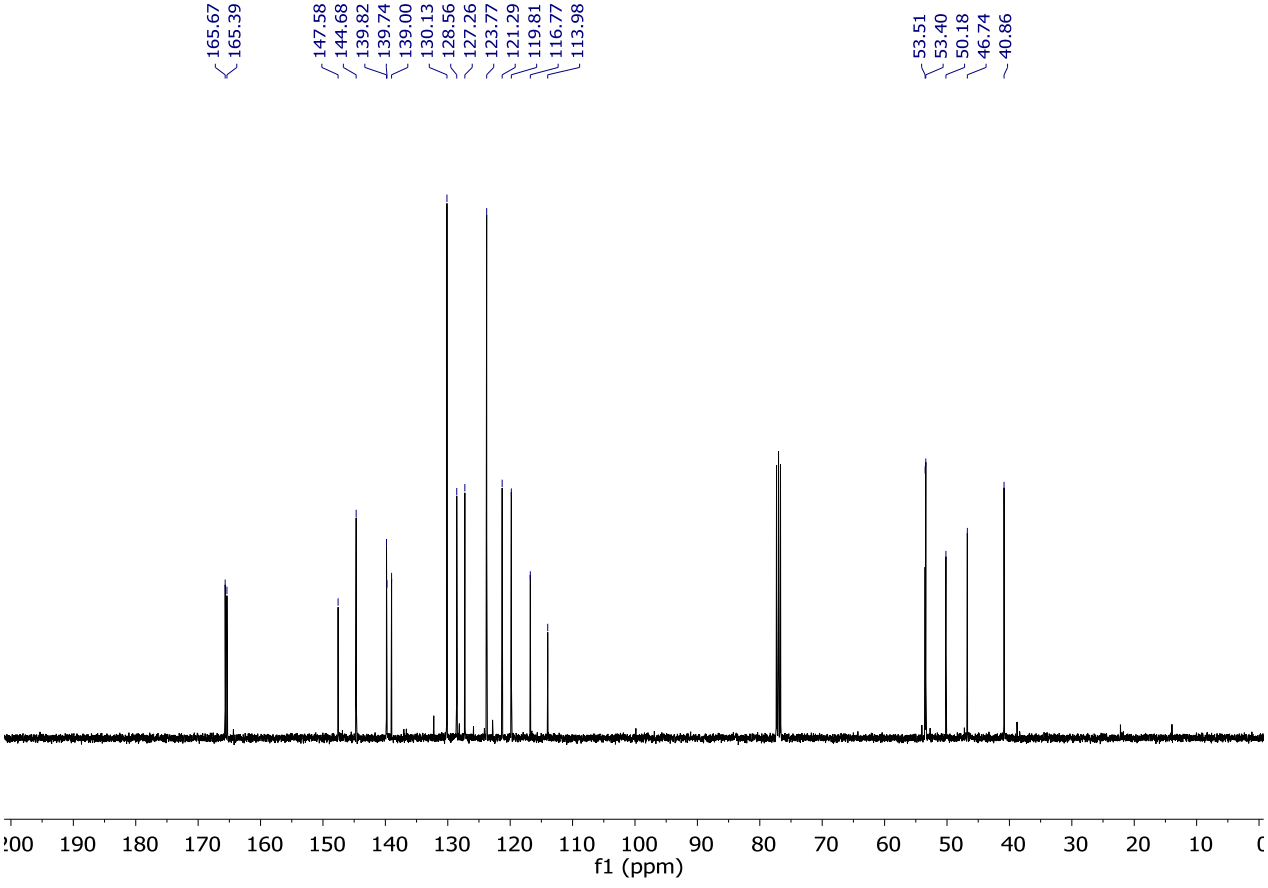

1.00
1.03
1.13
1.04
1.06
2.10
2.09
1.04
3.09
3.05
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

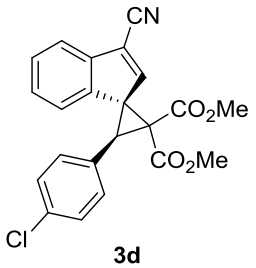

166.24
165.69
159.34
146.81
140.45
139.20
130.19
128.13
126.91
124.29
121.04
119.93
115.37
114.45
113.96
55.18
53.21
51.16
47.02
41.38
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me
O2N

**3c**

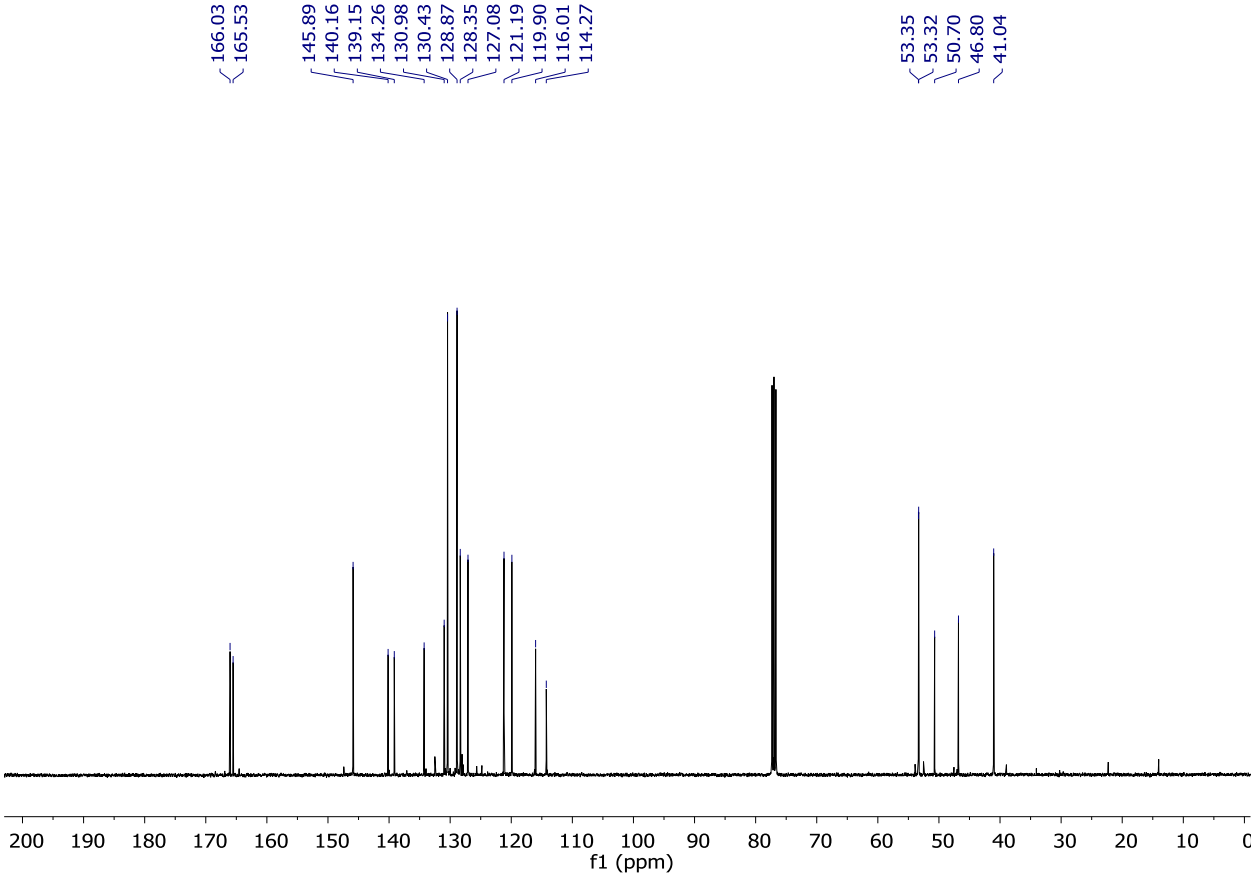

1.94
1.07
1.00
3.10
1.01
0.96
3.03
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

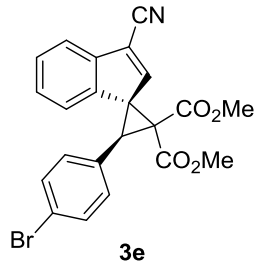

165.67
165.39
147.58
144.68
139.82
139.74
139.00
130.13
128.56
127.26
123.77
121.29
119.81
116.77
113.98
53.51
53.40
50.18
46.74
40.86
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
Cl

**3d**

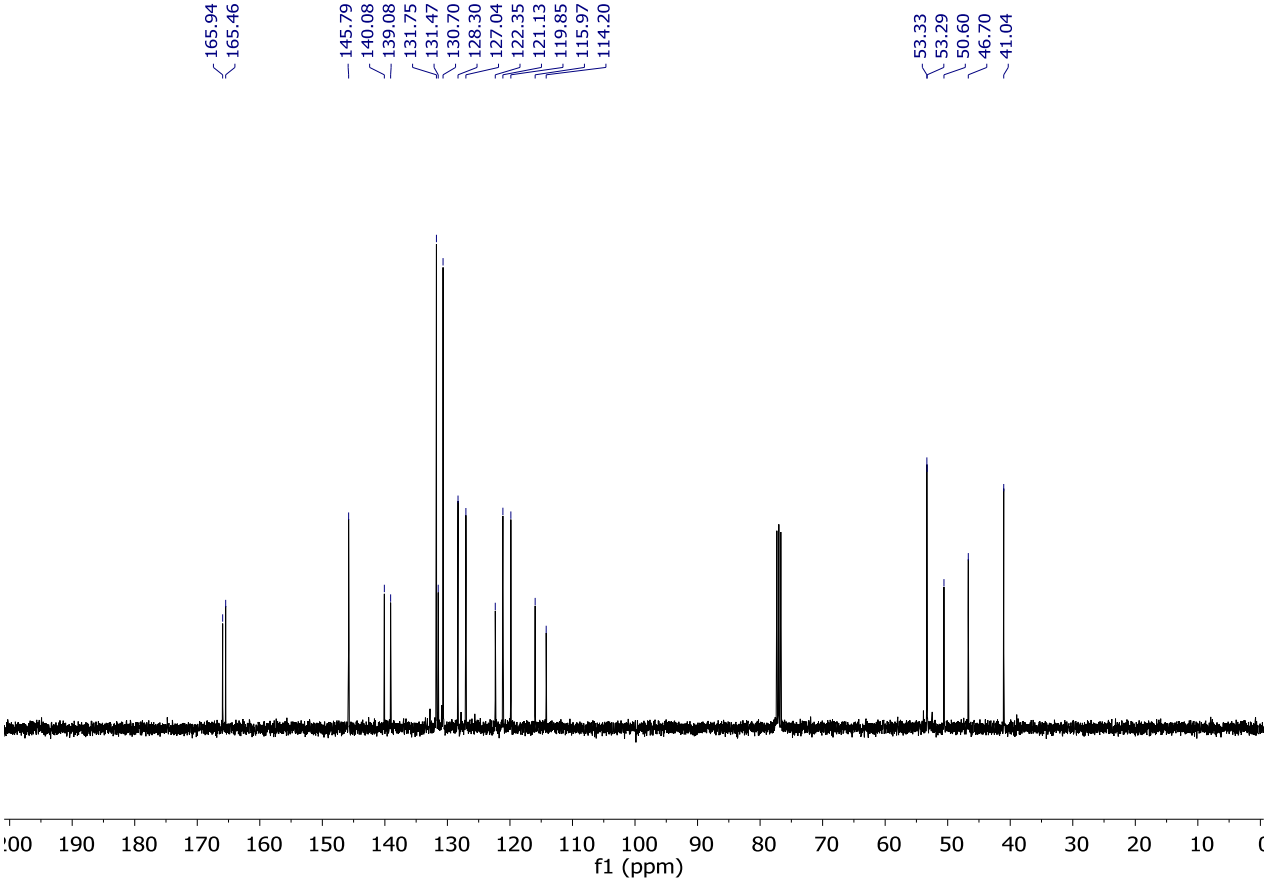

2.09
1.05
3.05
3.13
1.00
2.99
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

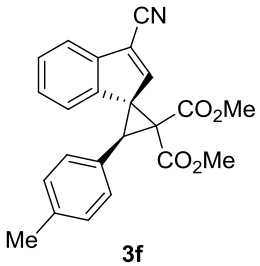

166.03
165.53
145.89
140.16
139.15
134.26
130.98
130.43
128.87
128.35
127.08
121.19
119.90
116.01
114.27
53.35
53.32
50.70
46.80
41.04
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me
Br

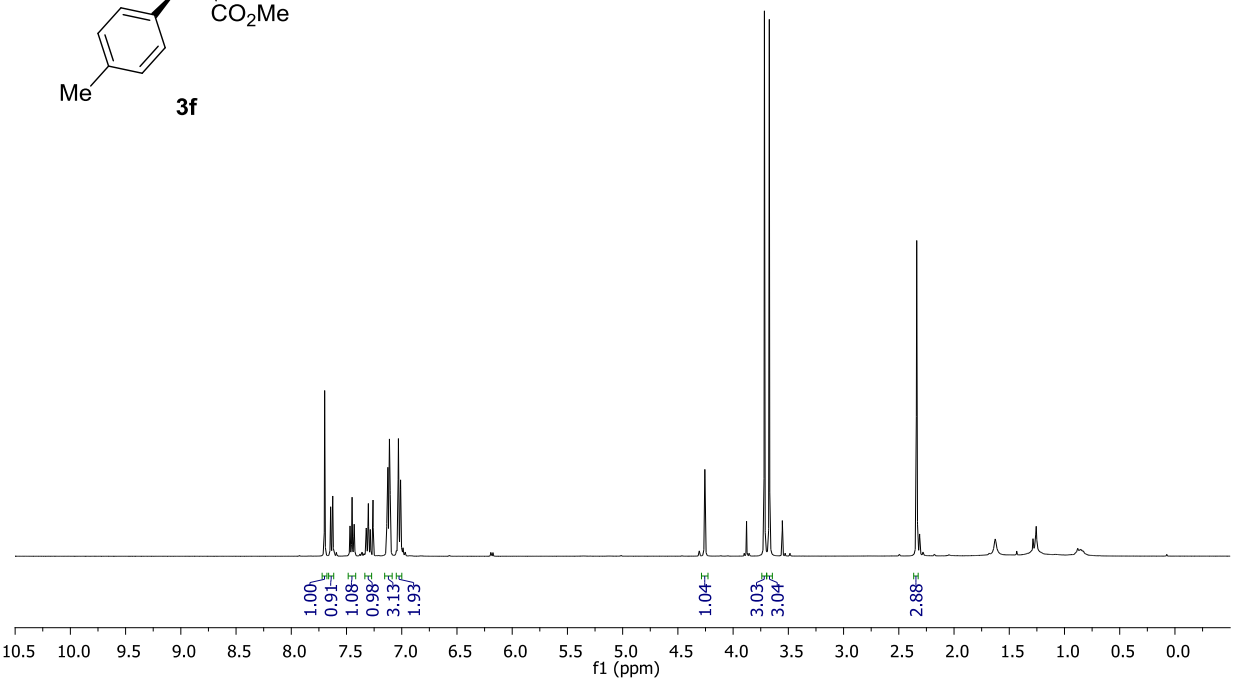
**3e**

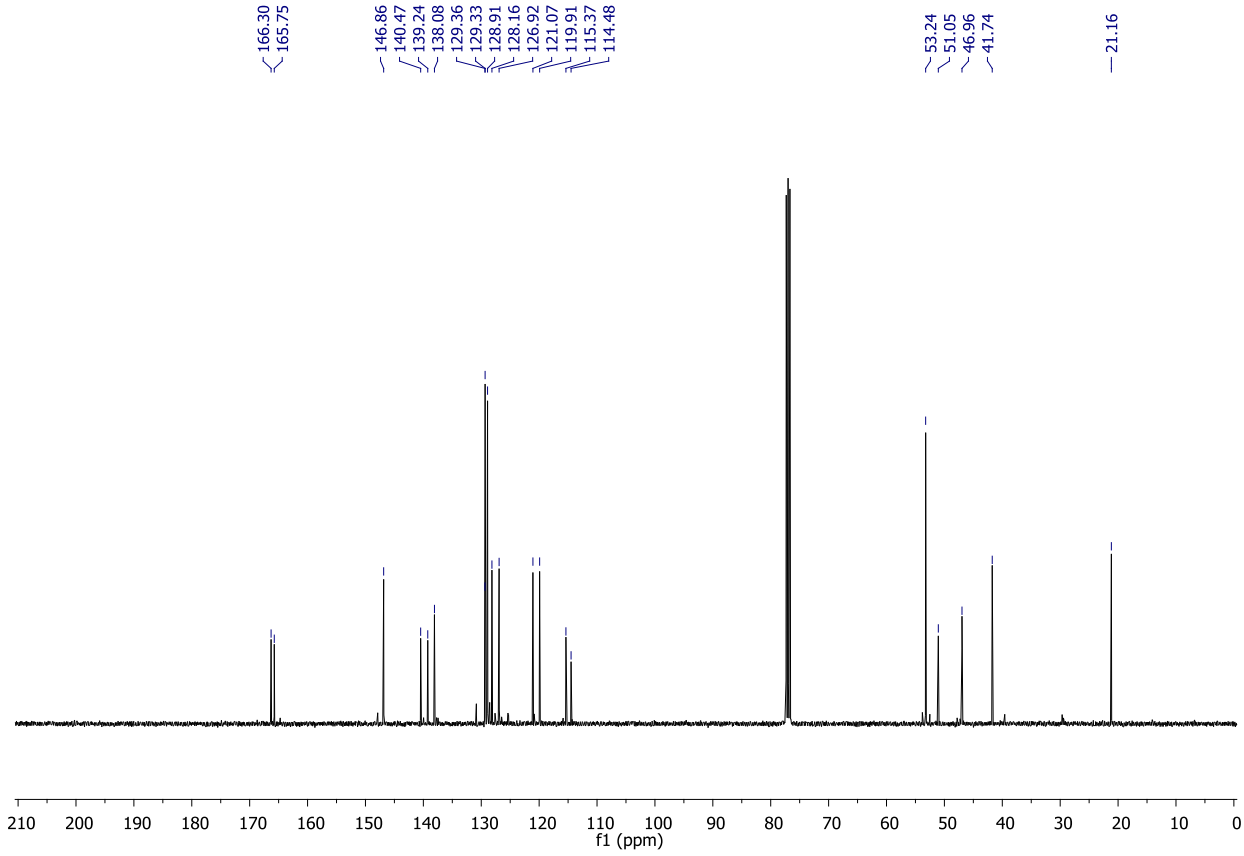

2.00
3.10
1.03
1.01
2.14
1.00
3.01
3.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

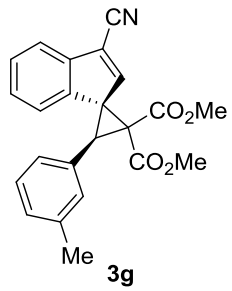

165.94
165.46
145.79
140.08
139.08
131.75
131.47
130.70
128.30
127.04
122.35
121.13
119.85
115.97
114.20
53.33
53.29
50.60
46.70
41.04
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
Me

**3f**

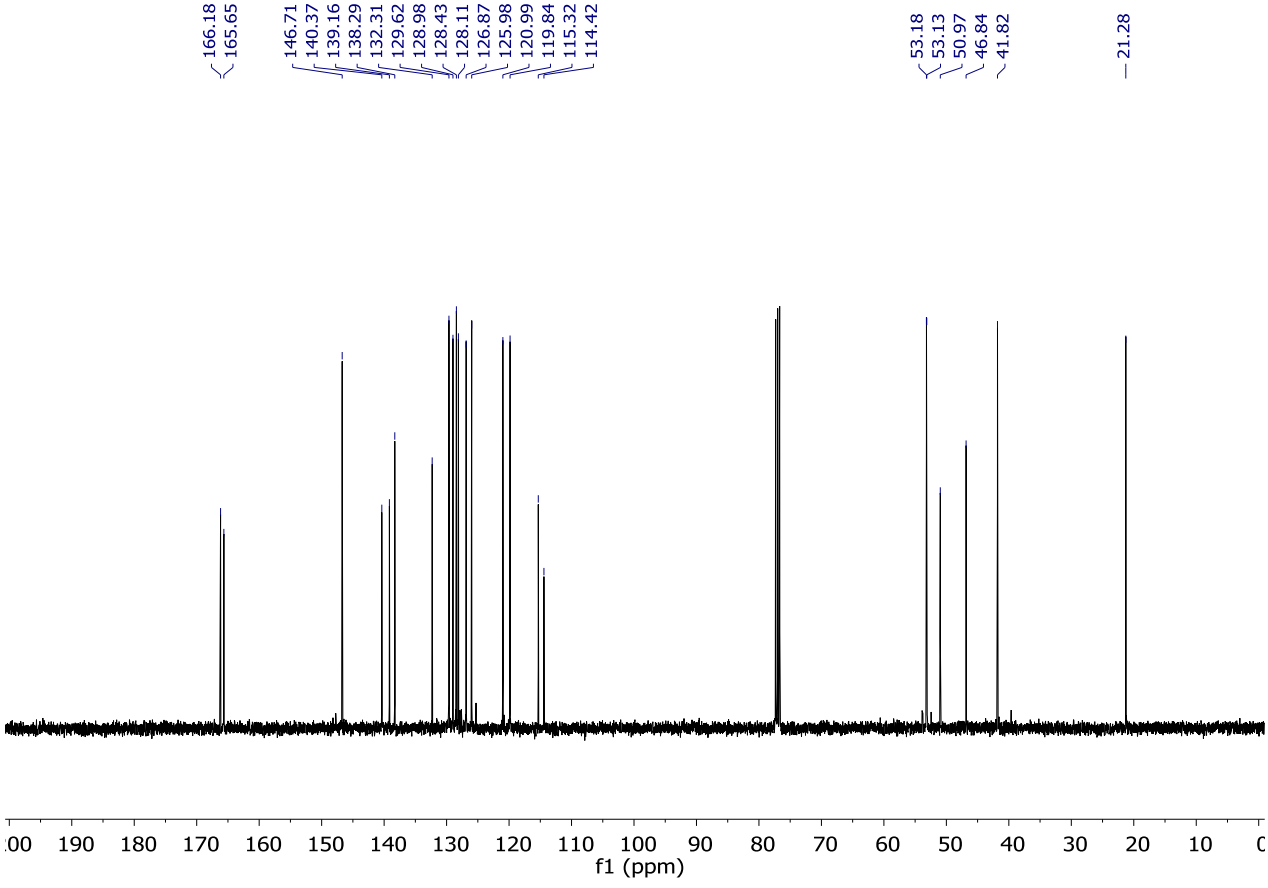

1.00
0.91
1.08
0.98
3.13
1.93
1.04
3.03
3.04
2.88
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

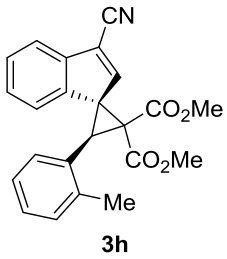

166.30
165.75
146.86
140.47
139.24
138.08
129.36
129.33
128.91
128.16
126.92
121.07
119.91
115.37
114.48
53.24
51.05
46.96
41.74
21.16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me
Me

**3g**

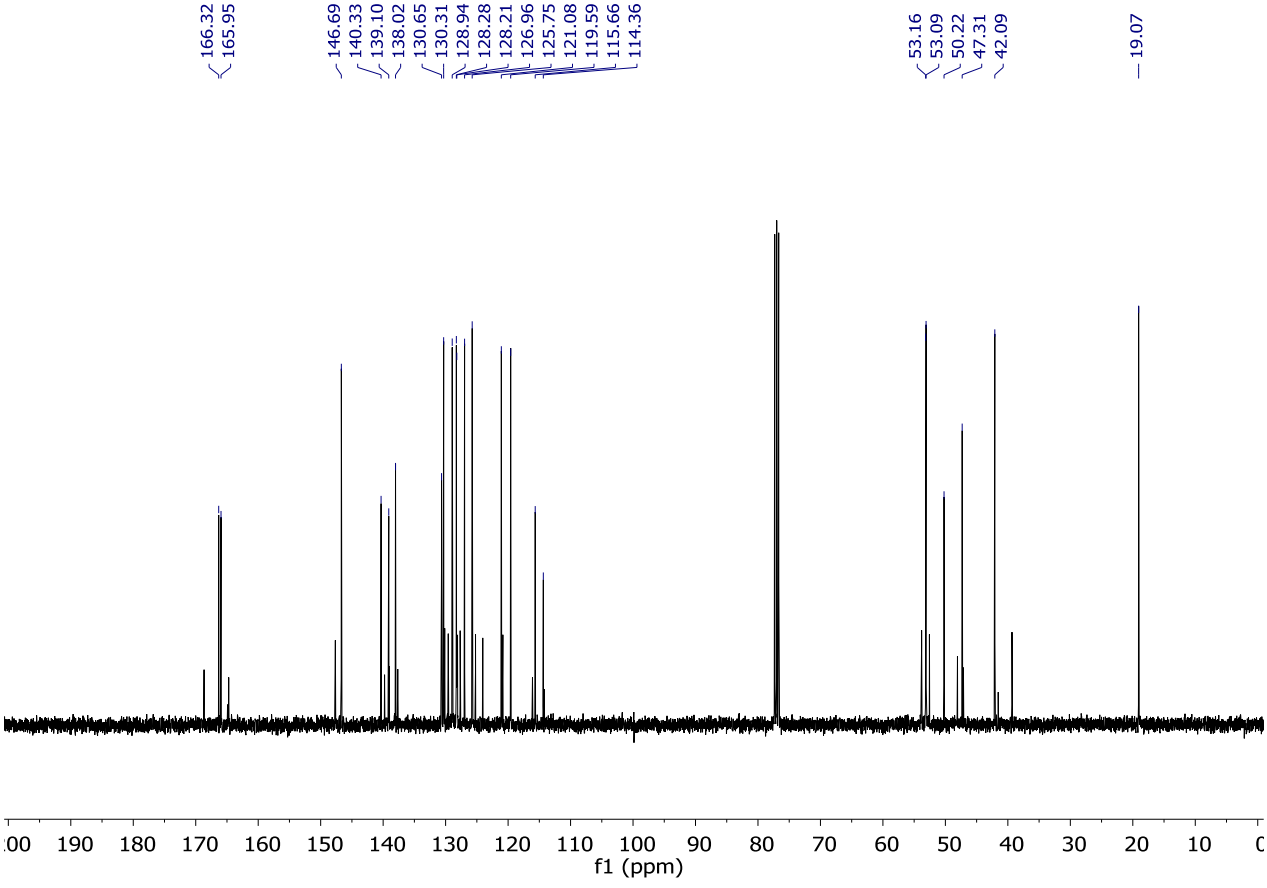

1.00
1.02
1.07
1.08
1.11
2.10
2.09
1.01
3.21
3.17
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

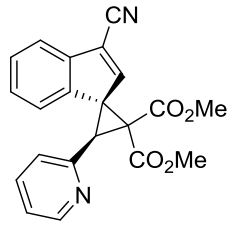

166.18
165.65
146.71
140.37
139.16
138.29
132.31
129.62
128.98
128.43
128.11
126.87
125.98
120.99
119.84
115.32
114.42
53.18
53.13
50.97
46.84
41.82
21.28
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
Me

**3h**

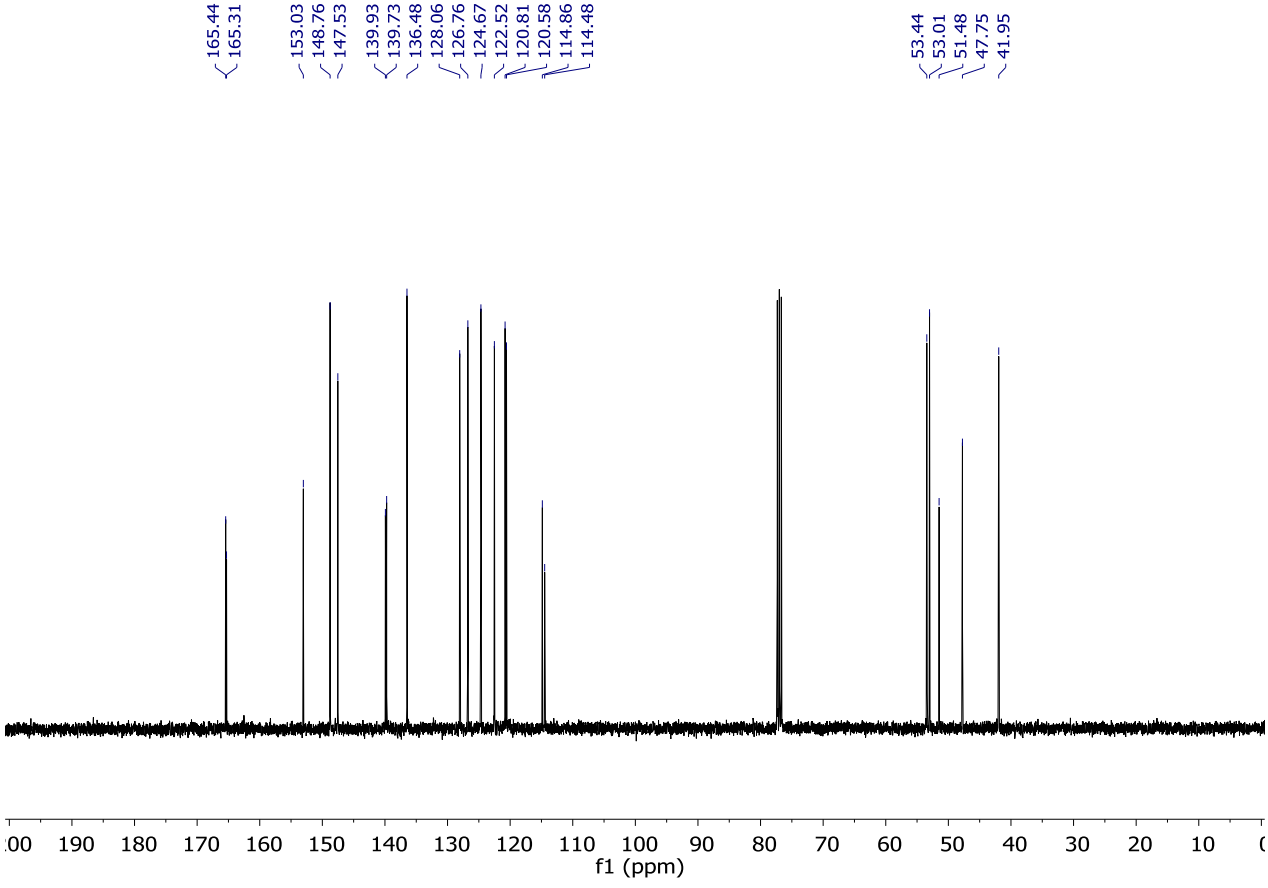

1.00
1.03
1.05
1.34
4.54
1.25
1.29
3.13
3.11
3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

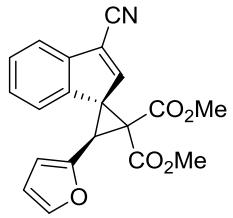

166.32
165.95
146.69
140.33
139.10
138.02
130.65
130.31
128.94
128.28
128.21
126.96
125.75
121.08
119.59
115.66
114.36
53.16
53.09
50.22
47.31
42.09
19.07
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
N

**3i**

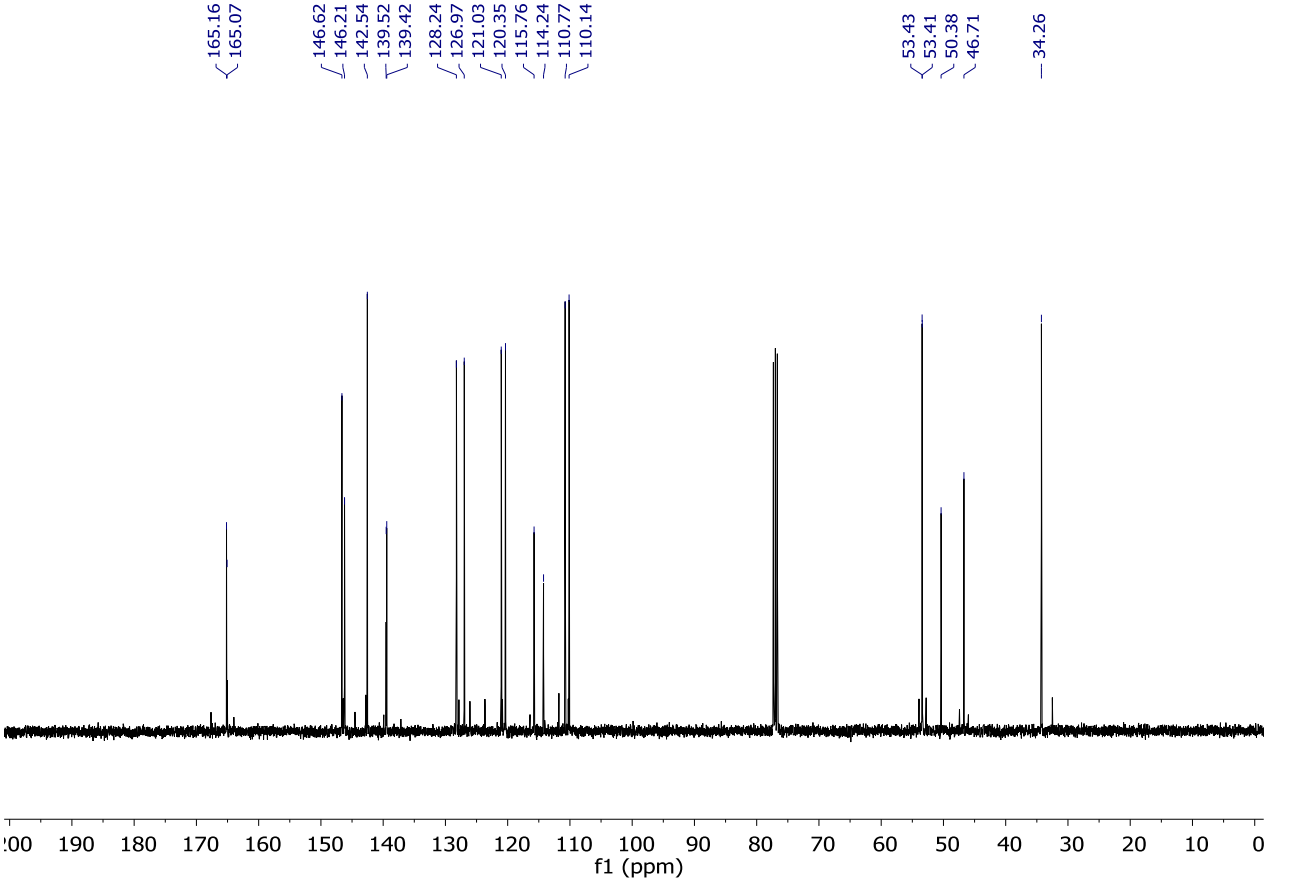

1.00
0.95
1.03
1.01
1.04
2.96
1.02
0.99
2.99
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

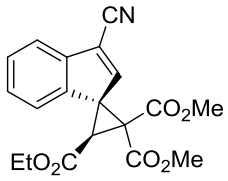

165.44
165.31
153.03
148.76
147.53
139.93
139.73
136.48
128.06
126.76
124.67
122.52
120.81
120.58
114.86
114.48
53.44
53.01
51.48
47.75
41.95
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
CO2Me
CO2Me
O

**3j**

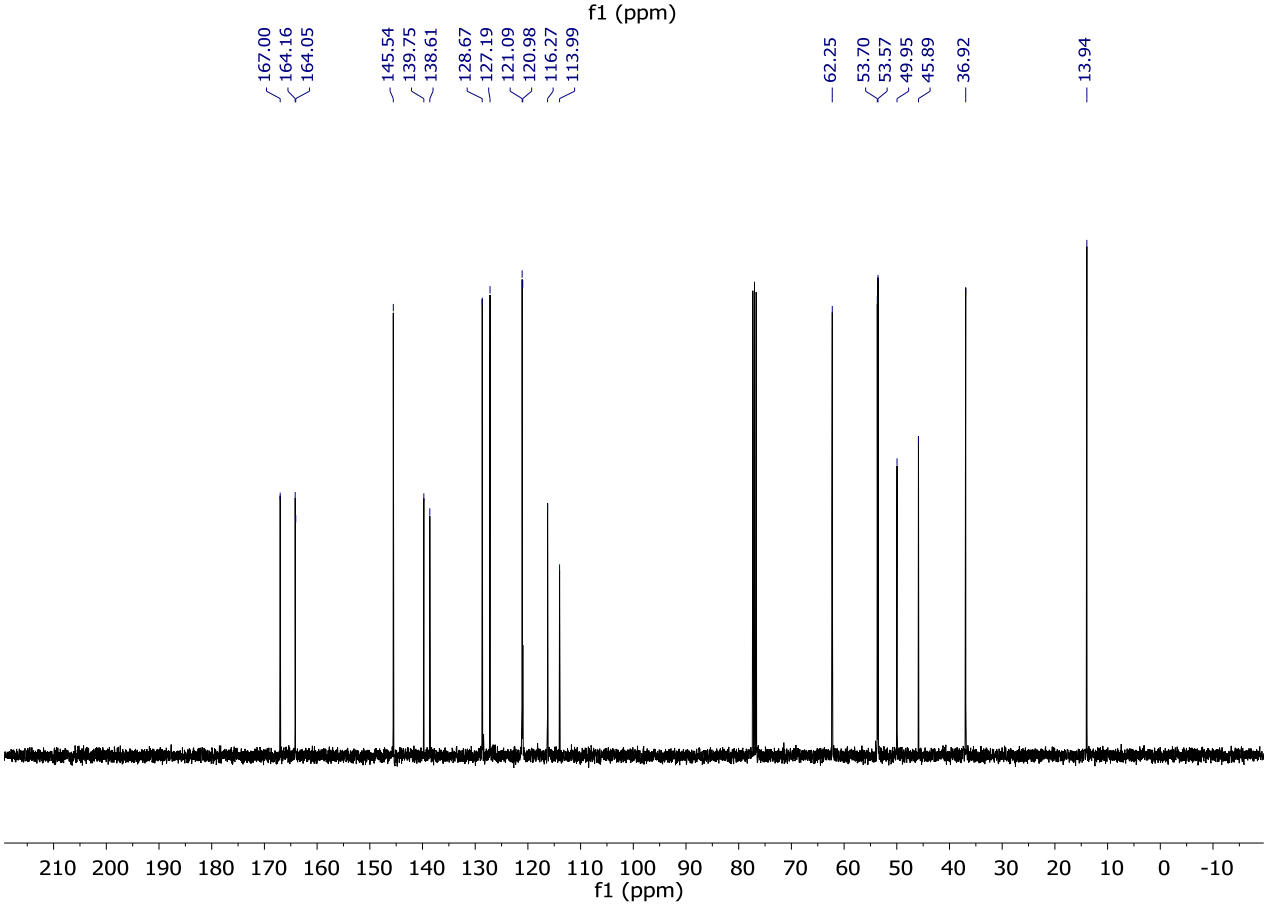

1.00
1.06
1.11
1.08
1.28
1.07
1.03
1.02
1.04
3.12
3.12
f1 (ppm)

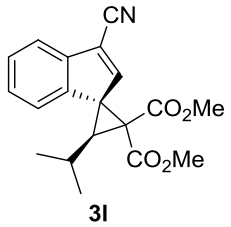

165.16
165.07
146.62
146.21
142.54
139.52
139.42
128.24
126.97
121.03
120.35
115.76
114.24
110.77
110.14
53.43
53.41
50.38
46.71
34.26
f1 (ppm)


CN
CO2Me
EtO2C
CO2Me

**3k**

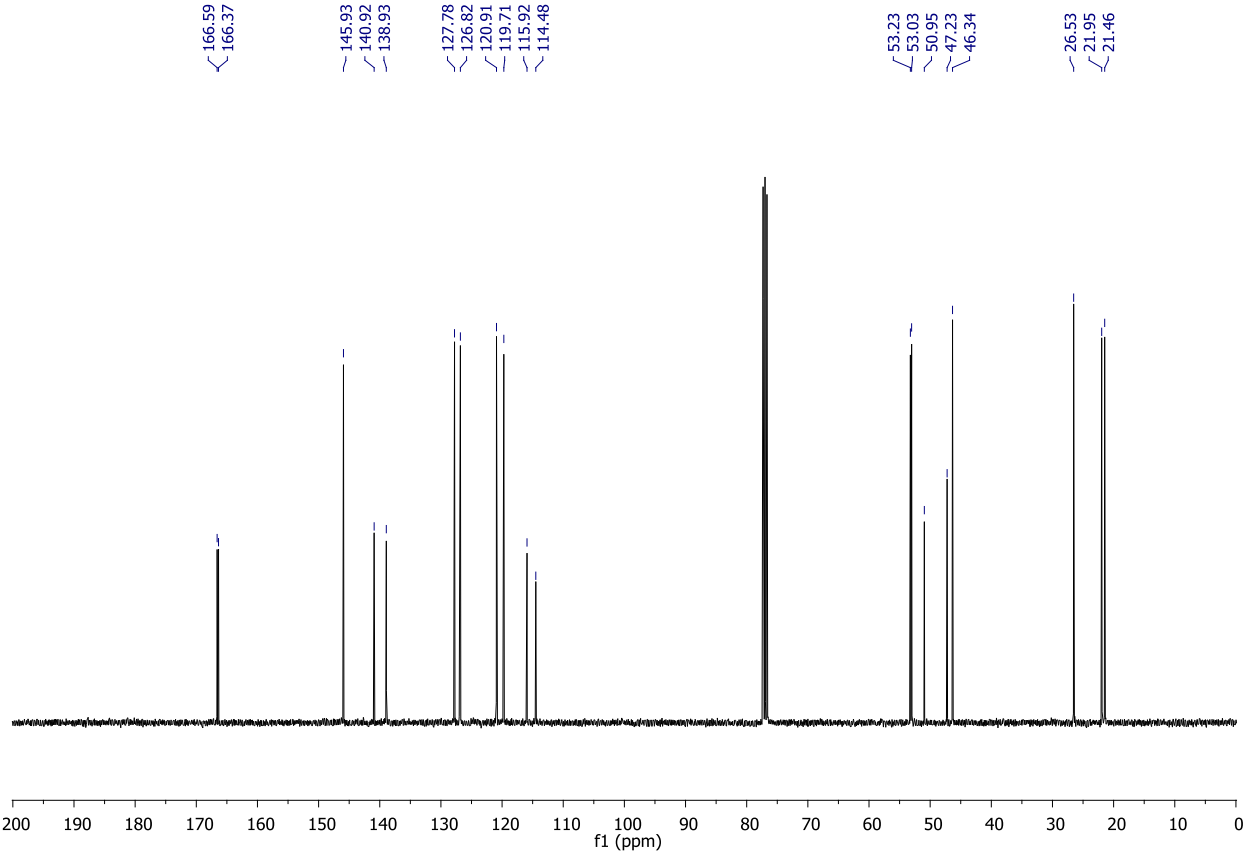

1.00
1.10
1.17
1.50
1.06
2.48
3.22
3.02
1.00
3.37
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

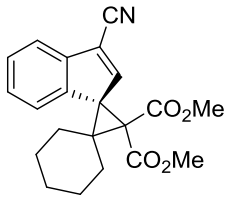

167.00
164.16
164.05
145.54
139.75
138.61
128.67
127.19
121.09
120.98
116.27
113.99
62.25
53.70
53.57
49.95
45.89
36.92
13.94
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CN
CO2Me
CO2Me

**3l**

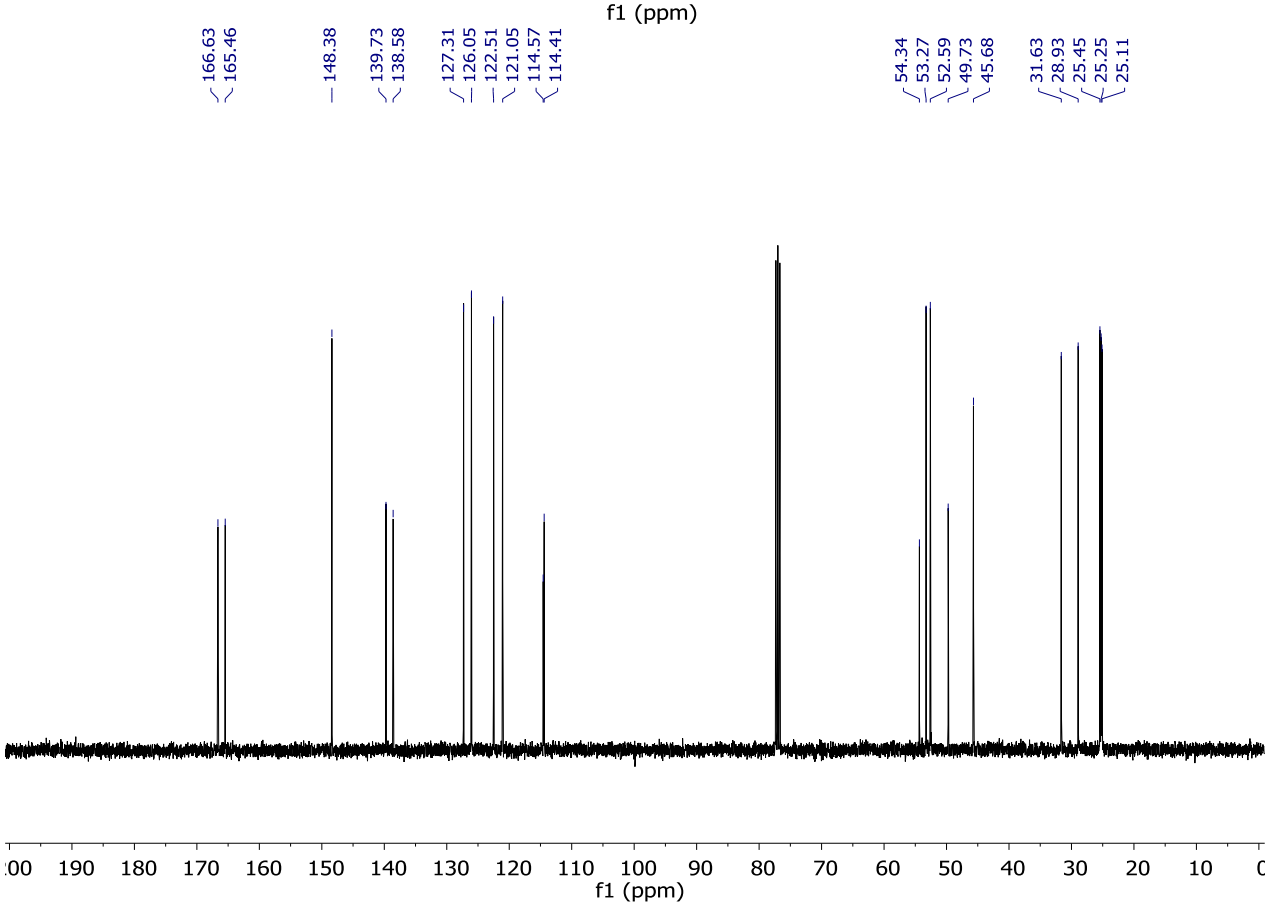

1.00
1.00
1.02
1.12
1.00
3.11
3.07
1.03
1.05
3.09
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

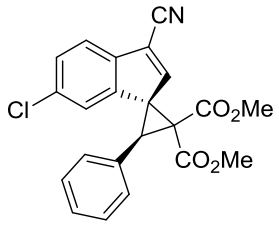

166.59
166.37
145.93
140.92
138.93
127.78
126.82
120.91
119.71
115.92
114.48
53.23
53.03
50.95
47.23
46.34
26.53
21.95
21.46
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me

**3m**

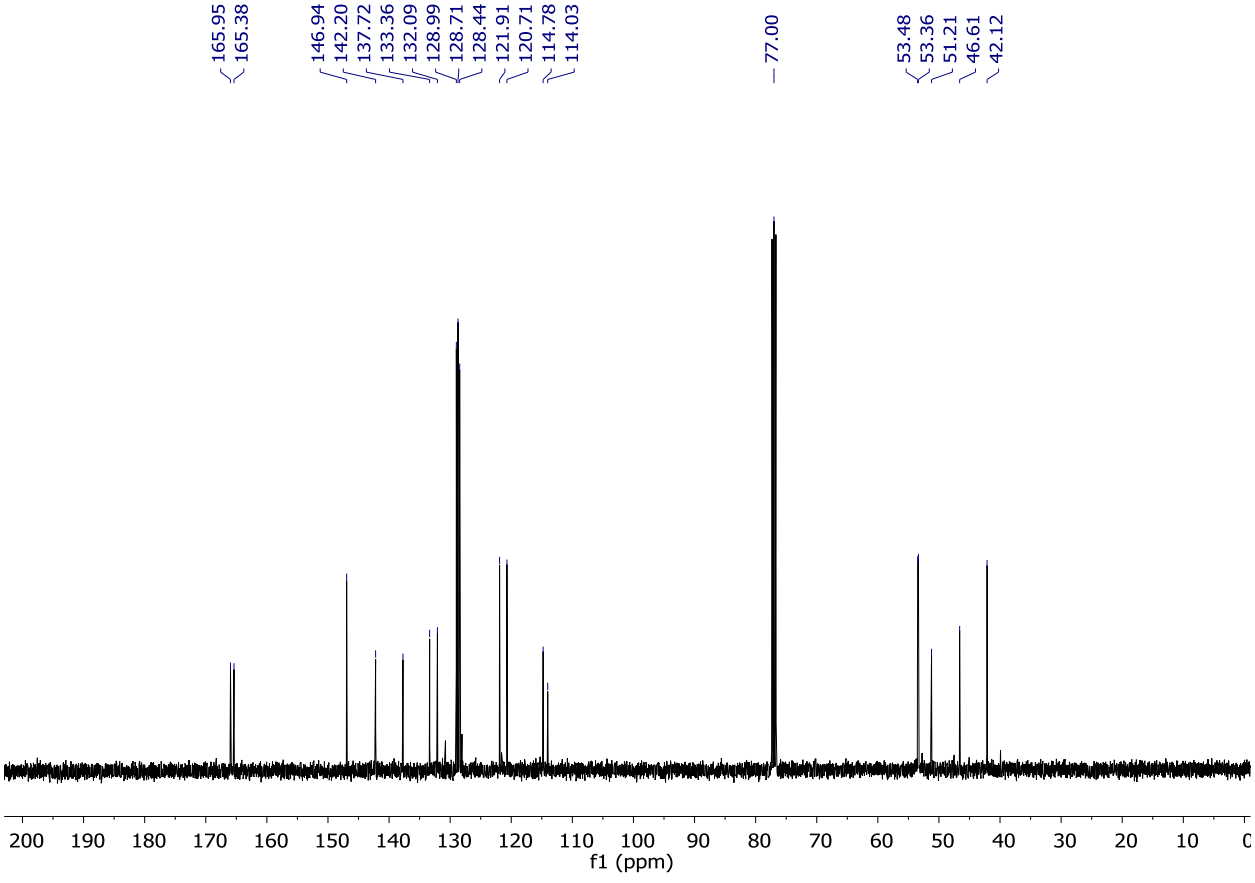

1.00
1.01
1.04
1.04
1.01
3.09
3.07
2.11
2.13
2.16
2.20
1.15
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

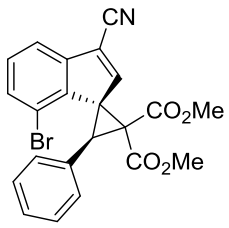

166.63
165.46
148.38
139.73
138.58
127.31
126.05
122.51
121.05
114.57
114.41
54.34
53.27
52.59
49.73
45.68
31.63
28.93
25.45
25.25
25.11
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CN
Cl
CO2Me
CO2Me

**3n**

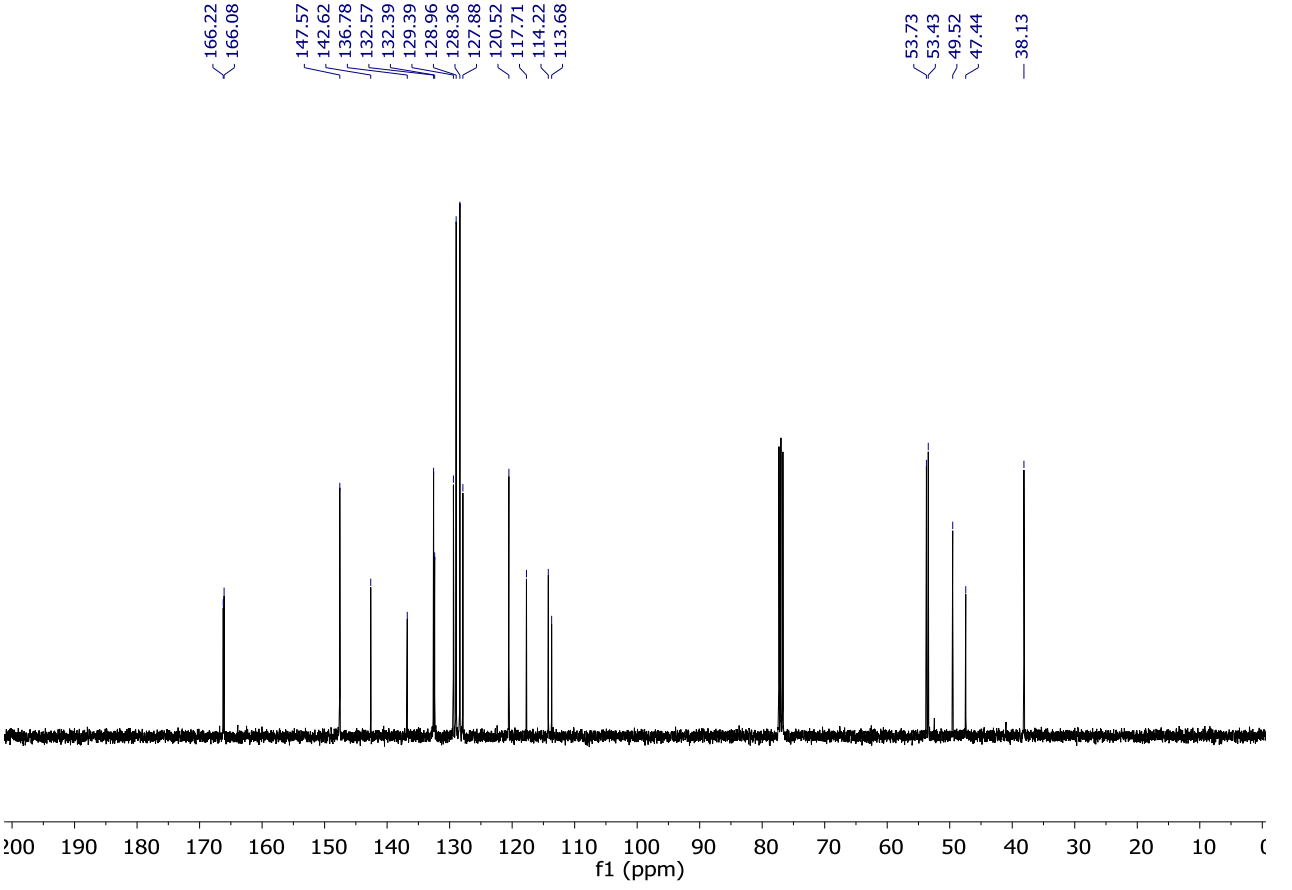

1.00
1.01
1.03
3.15
3.12
1.04
2.95
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

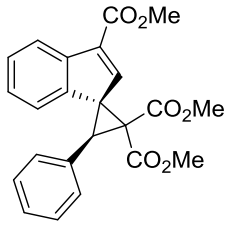

165.95
165.38
146.94
142.20
137.72
133.36
132.09
128.99
128.71
128.44
121.91
120.71
114.78
114.03
77.00
53.48
53.36
51.21
46.61
42.12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
Br
CO2Me

**3o**

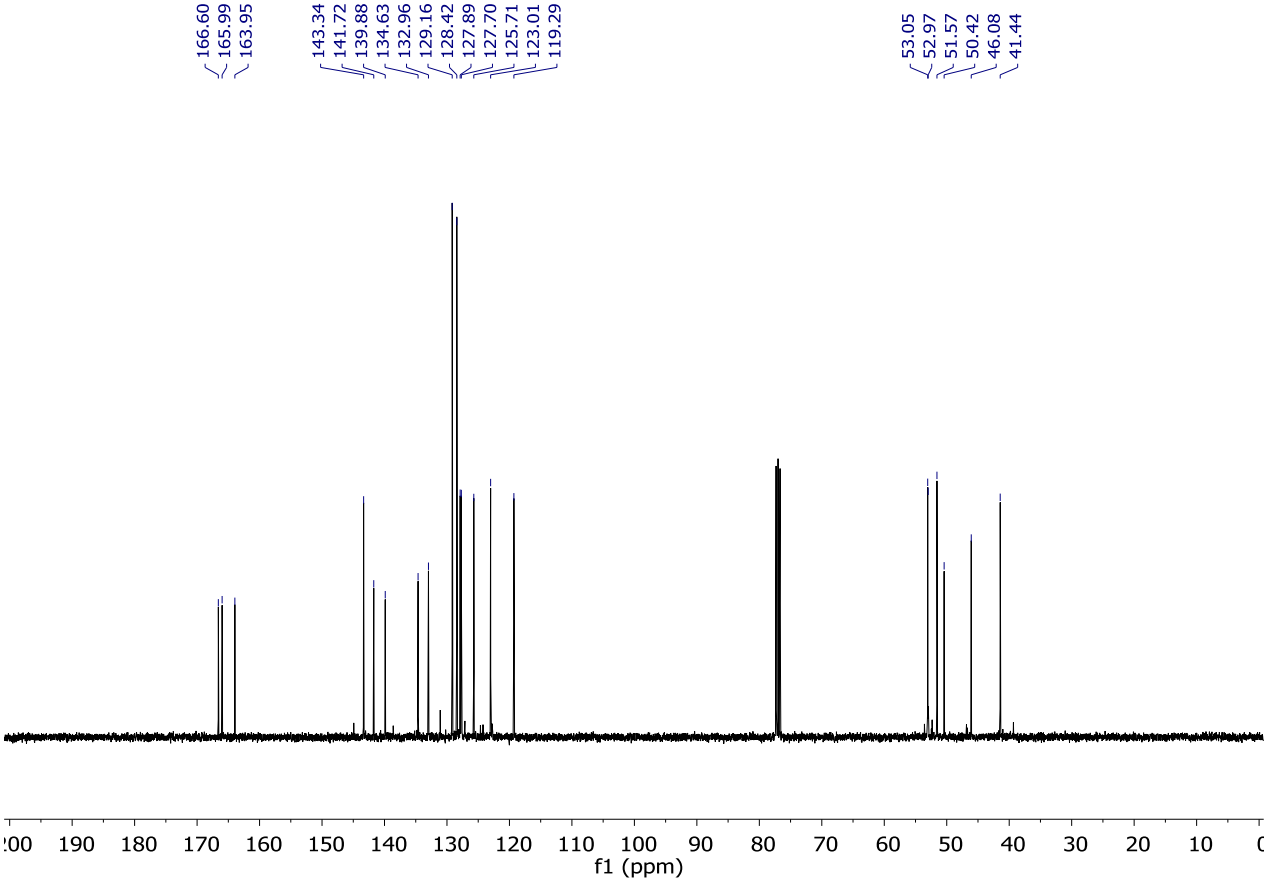

1.89
1.00
3.00
1.09
1.95
0.94
2.87
2.86
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

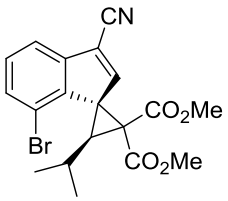

166.22
166.08
147.57
142.62
136.78
132.57
132.39
129.39
128.96
128.36
127.88
120.52
117.71
114.22
113.68
53.73
53.43
49.52
47.44
38.13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


CO2Me
CO2Me
CO2Me

**3p**

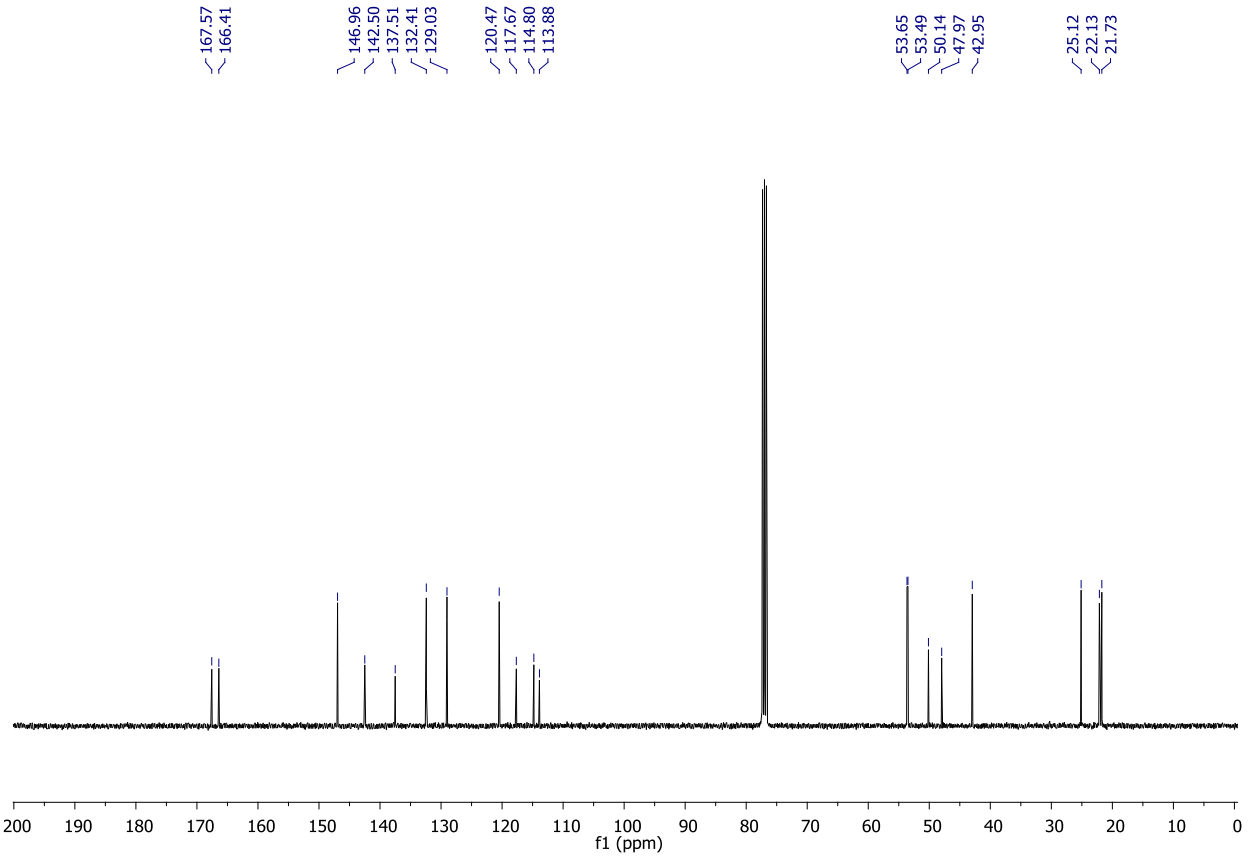

1.00
0.93
1.19
3.24
1.36
2.12
1.02
1.04
2.98
3.16
3.17
f1 (ppm)

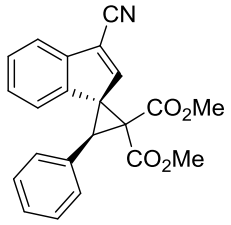

166.60
165.99
163.95
143.34
141.72
139.88
134.63
132.96
129.16
128.42
127.89
127.70
125.71
123.01
119.29
53.05
52.97
51.57
50.42
46.08
41.44
f1 (ppm)


CN
CO2Me
Br
CO2Me

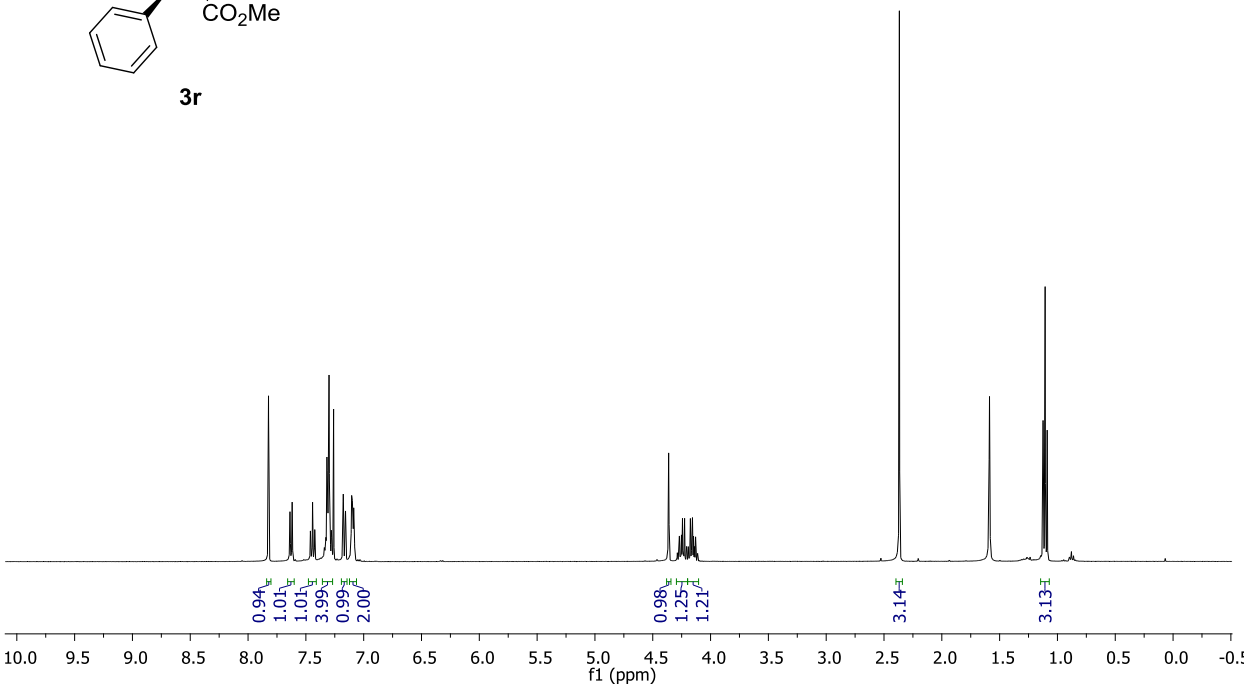
**3q**

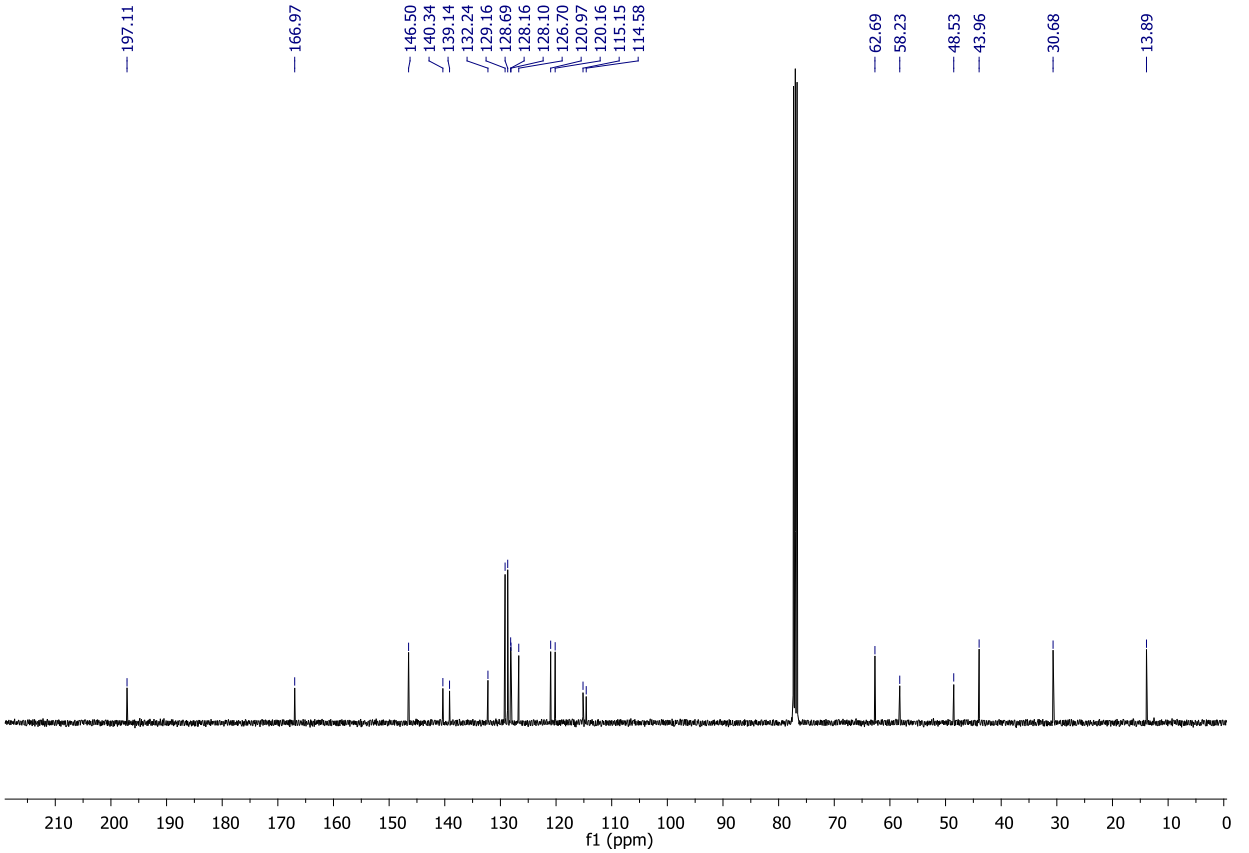

1.01
0.98
1.00
1.02
0.96
6.12
1.17
3.03
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

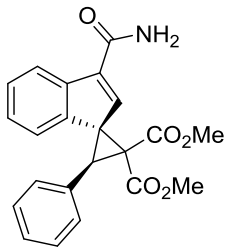

167.57
166.41
146.96
142.50
137.51
132.41
129.03
120.47
117.67
114.80
113.88
53.65
53.49
50.14
47.97
42.95
25.12
22.13
21.73
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CO2Me
CO2Me

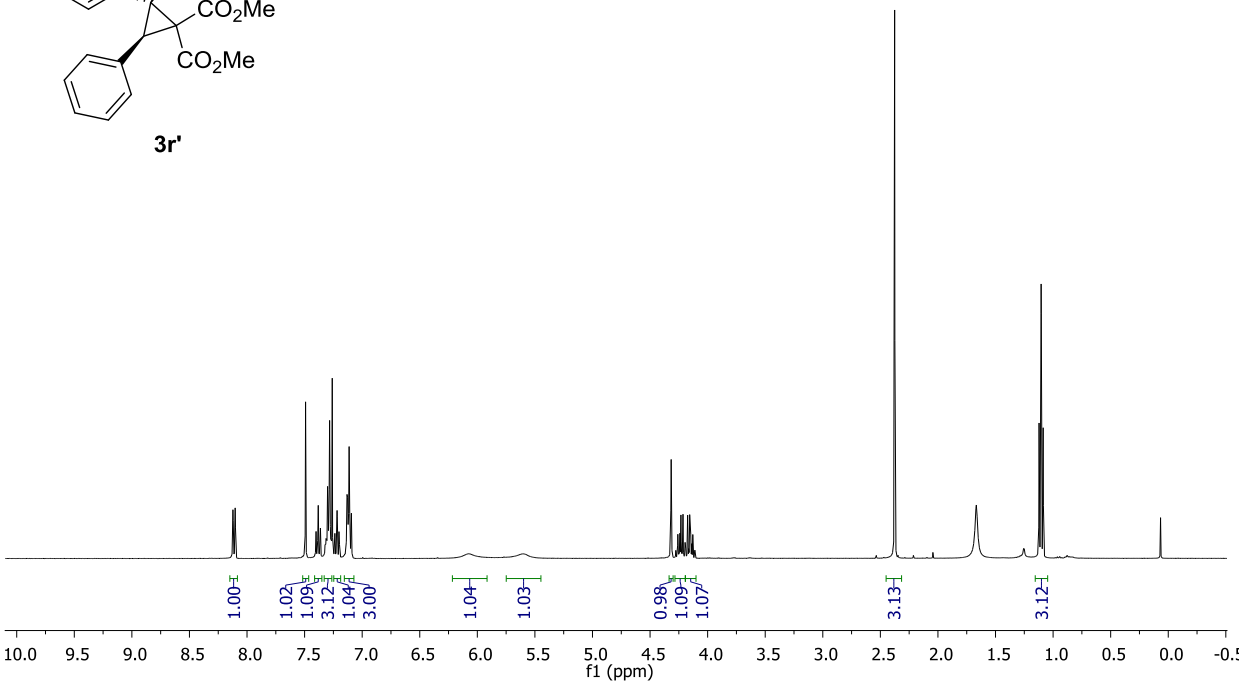
**3r**

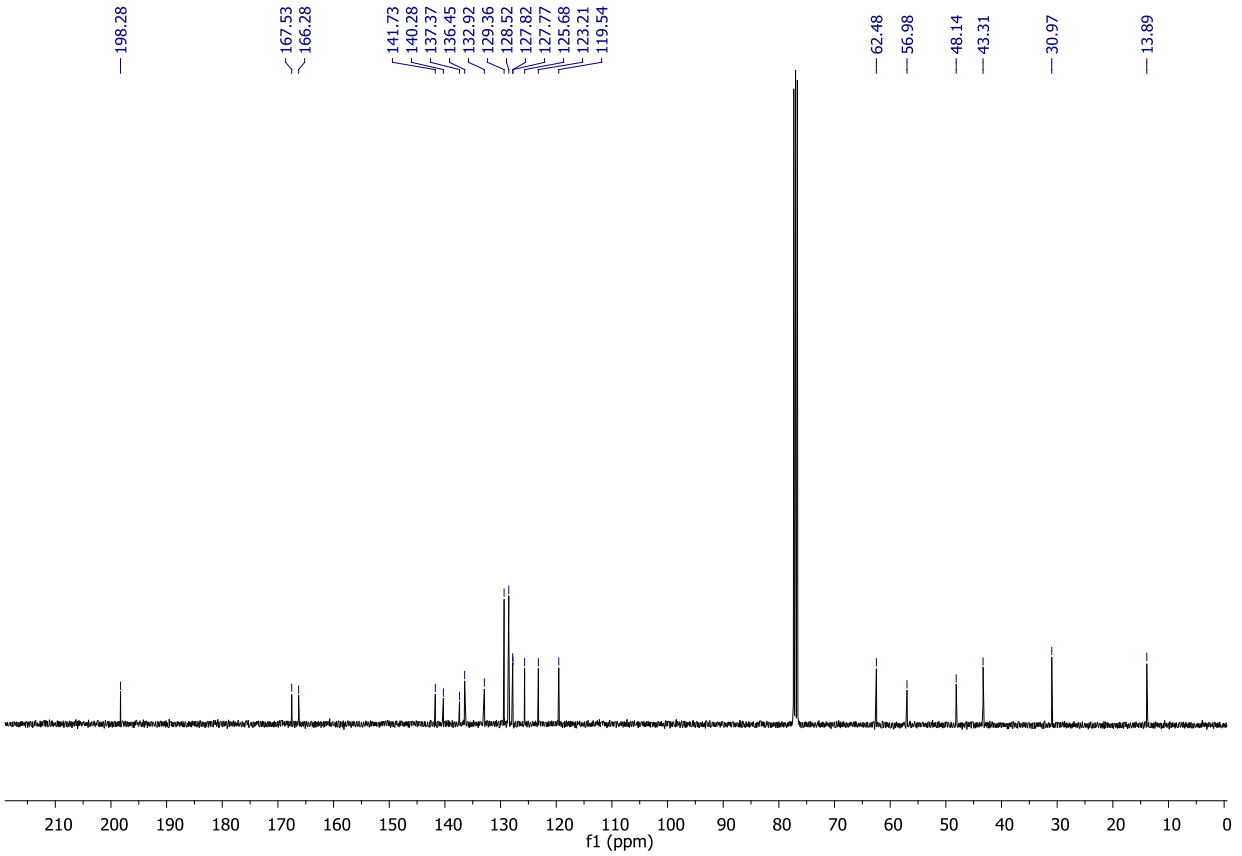

0.94
1.01
1.01
3.99
0.99
2.00
0.98
1.25
1.21
3.14
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


197.11
166.97
146.50
140.34
139.14
132.24
129.16
128.69
128.16
128.10
126.70
120.97
120.16
115.15
114.58
62.69
58.23
48.53
43.96
30.68
13.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

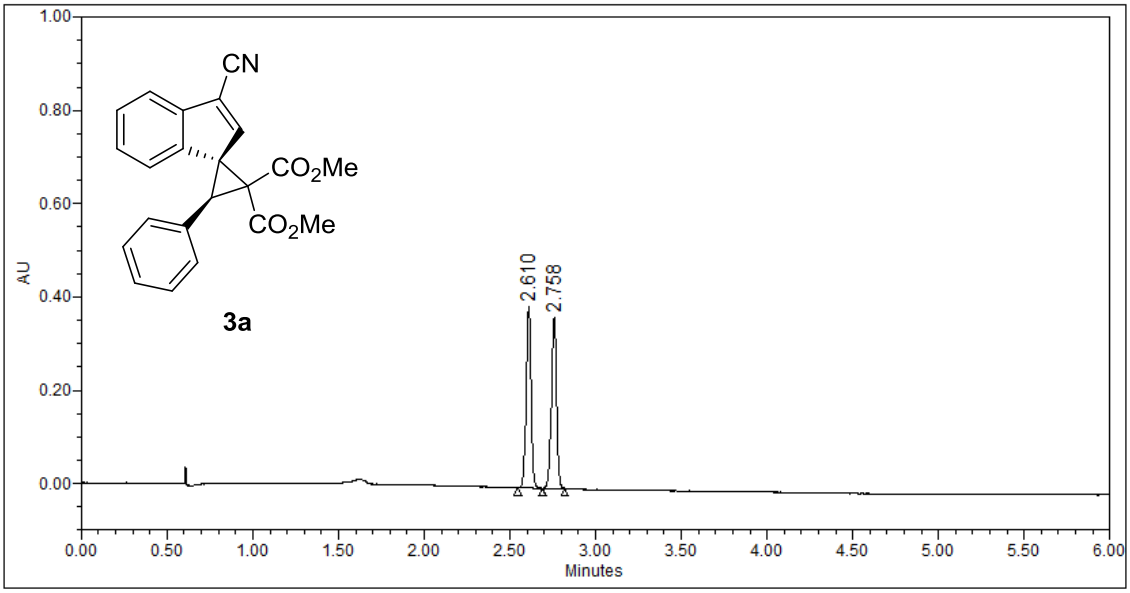

O
NH2
CO2Me
CO2Me

**3r'**

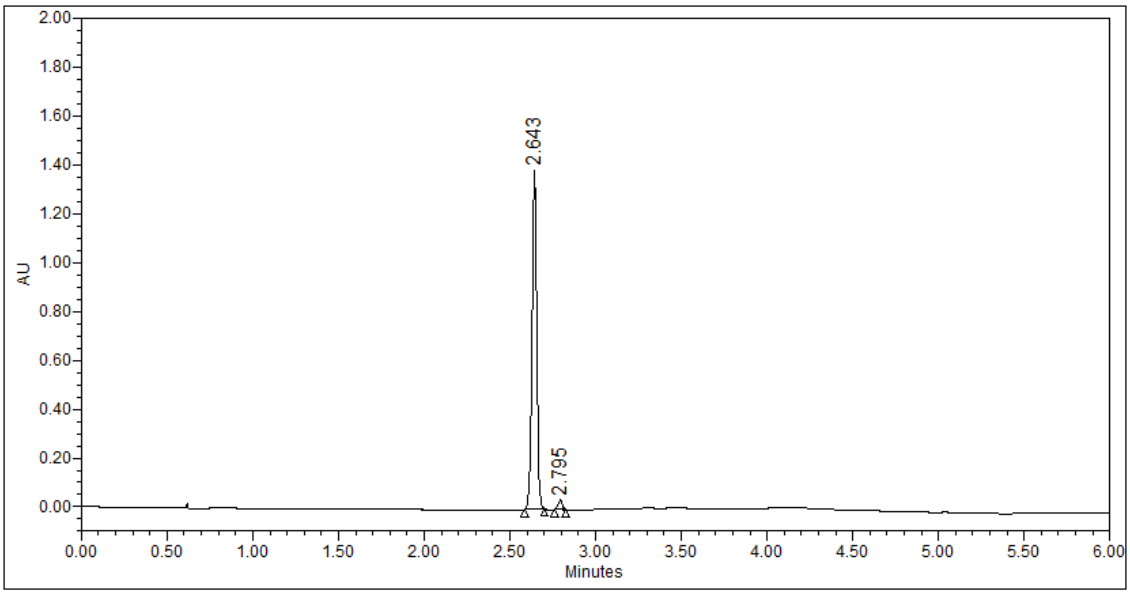

1.00
1.02
1.09
3.12
1.04
3.00
1.04
1.03
0.98
1.09
1.07
3.13
3.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


198.28
167.53
166.28
141.73
140.28
137.37
136.45
132.92
129.36
128.52
127.82
127.77
125.68
123.21
119.54
62.48
56.98
48.14
43.31
30.97
13.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

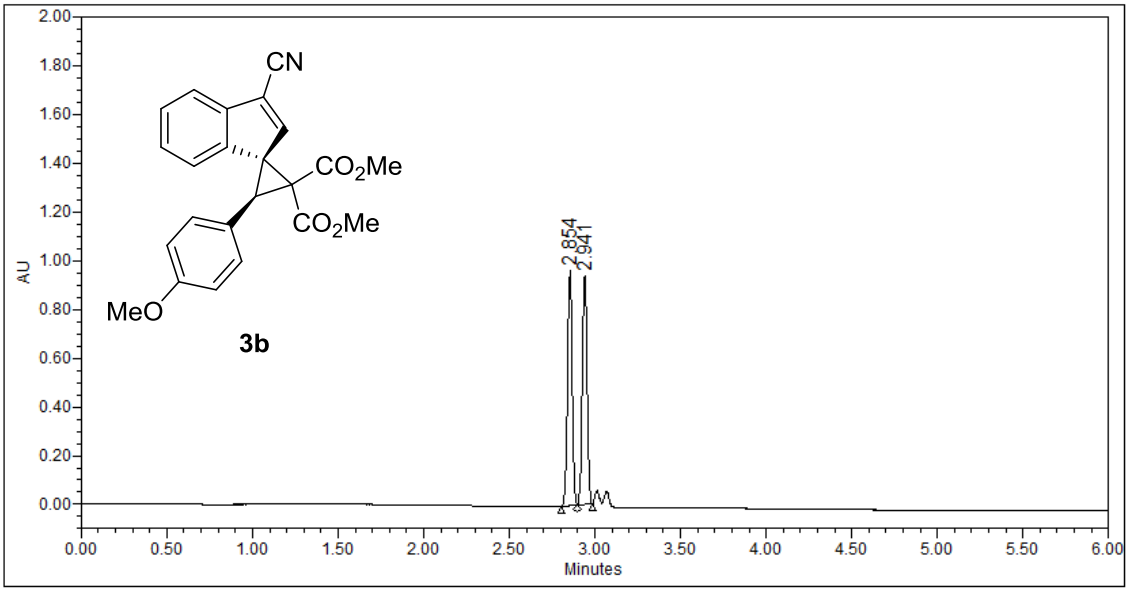
## 9. UPC$^2$ traces



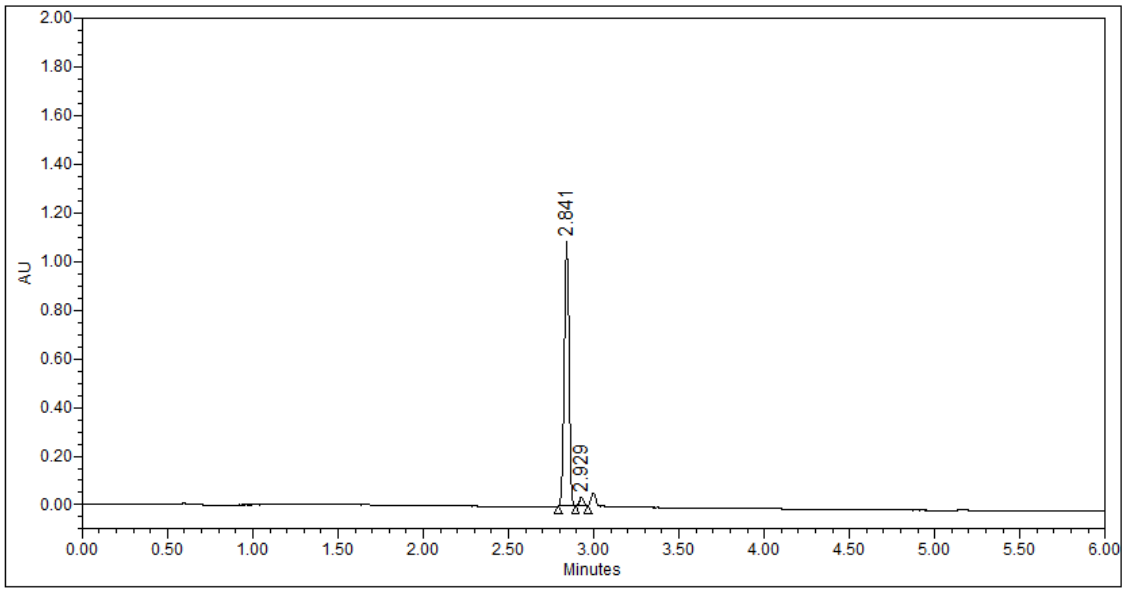

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.610 | 50.07 |
| 2 | 2.758 | 49.93 |



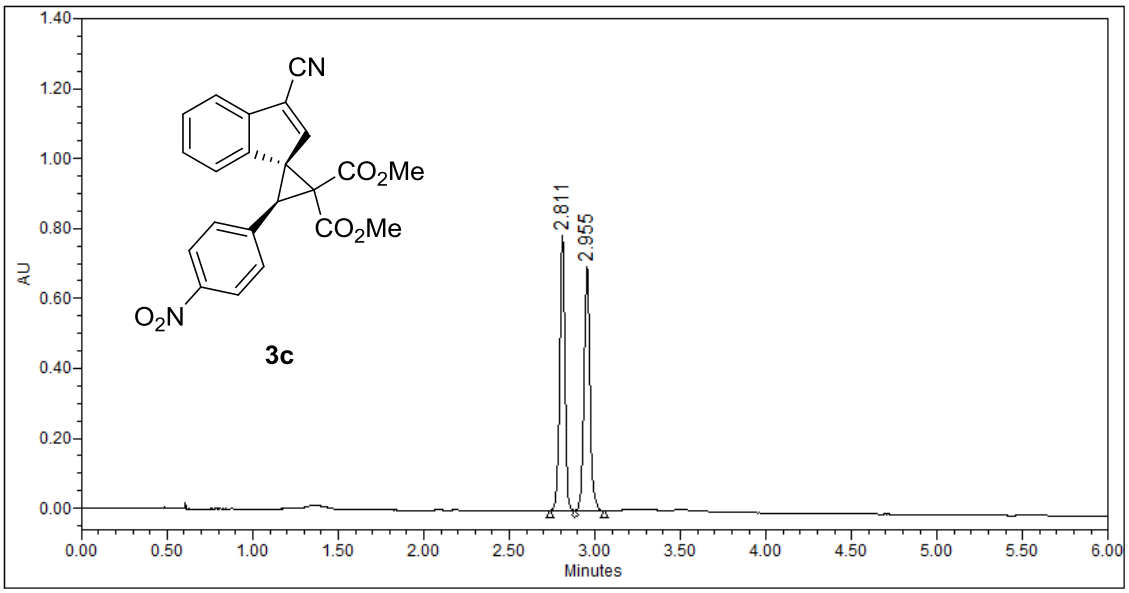

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.643 | 97.46 |
| 2 | 2.795 | 2.54 |



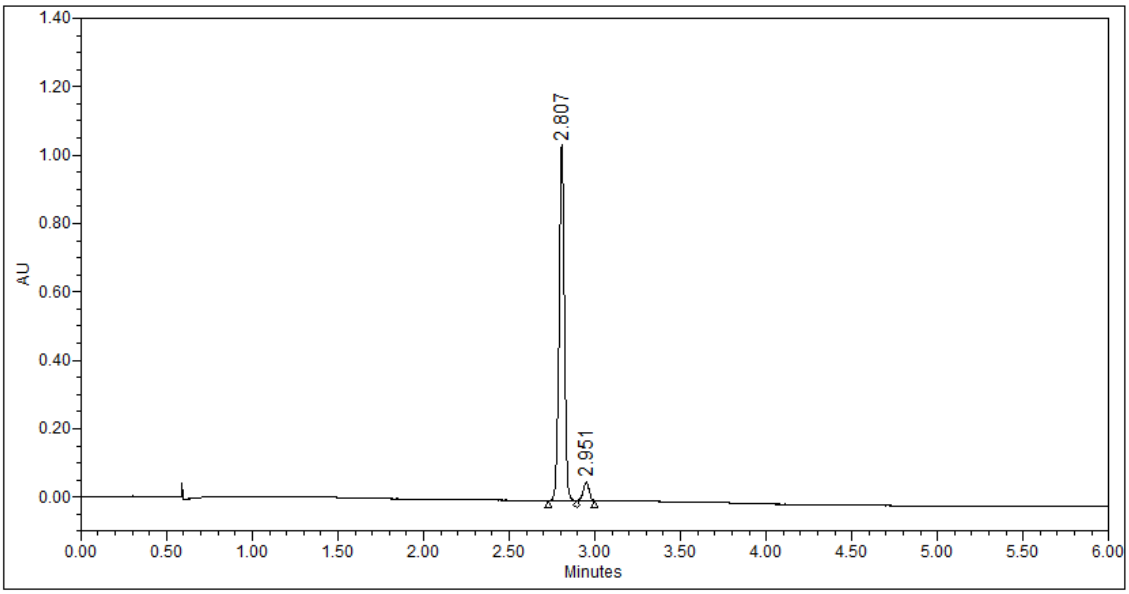

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.854 | 50.26 |
| 2 | 2.941 | 49.74 |



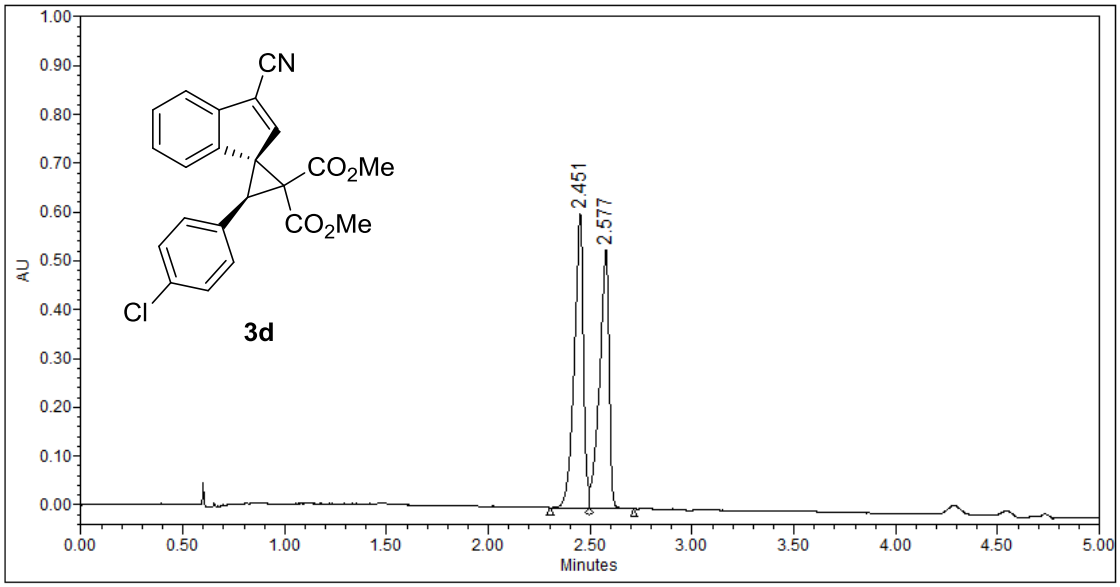

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.841 | 97.10 |
| 2 | 2.929 | 2.90 |



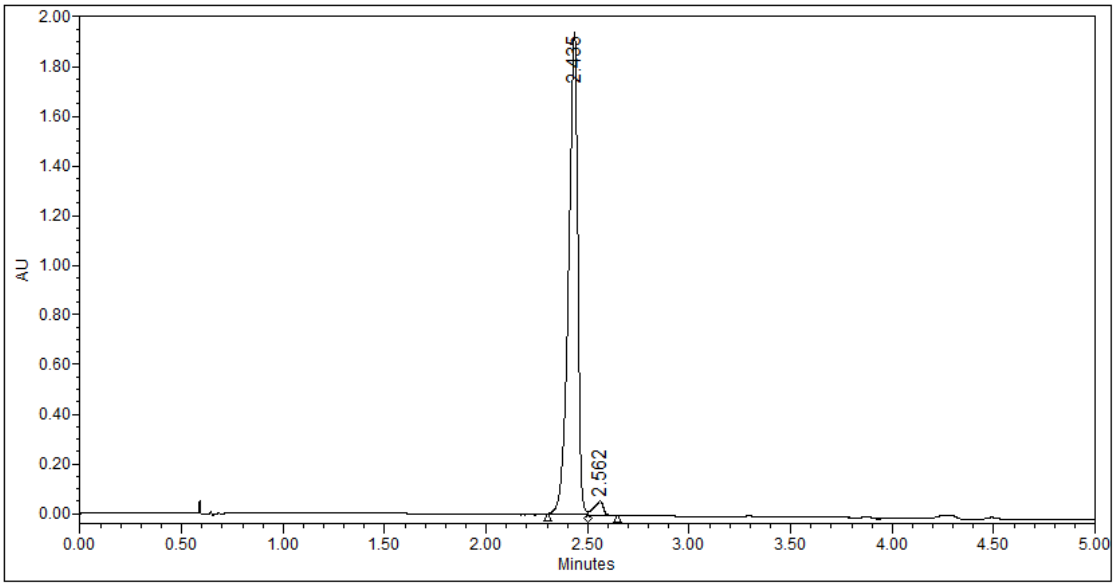

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.811 | 49.96 |
| 2 | 2.955 | 50.04 |



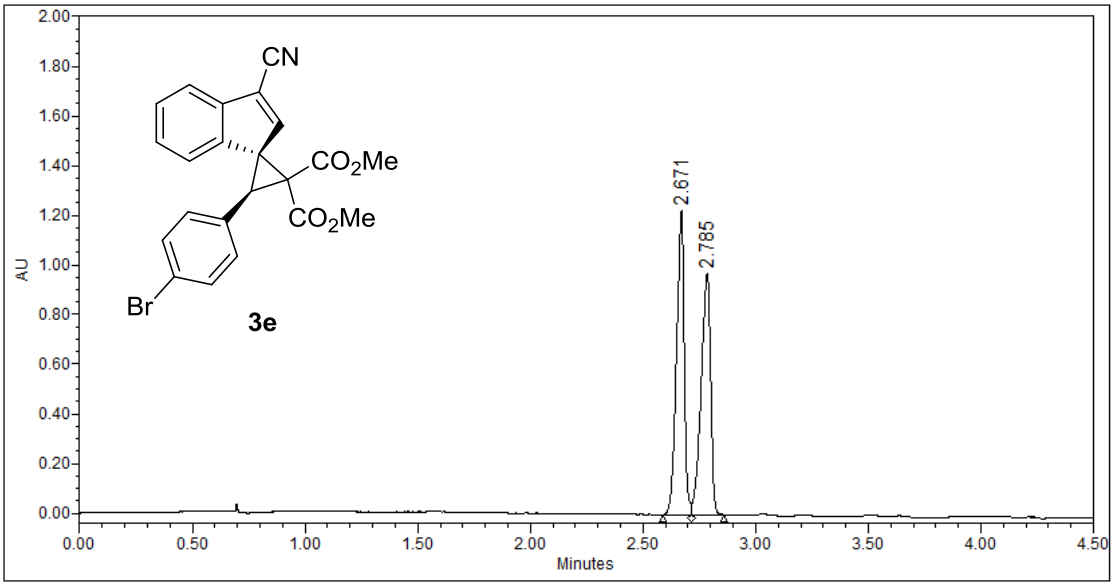

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.807 | 94.68 |
| 2 | 2.951 | 5.32 |



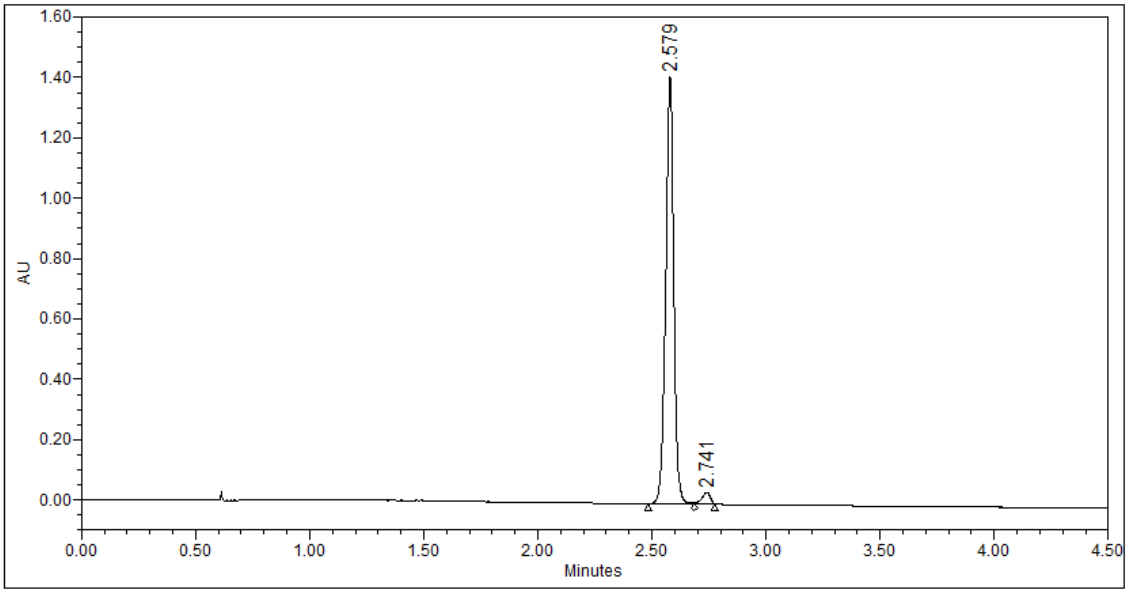

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.451 | 52.35 |
| 2 | 2.577 | 47.65 |



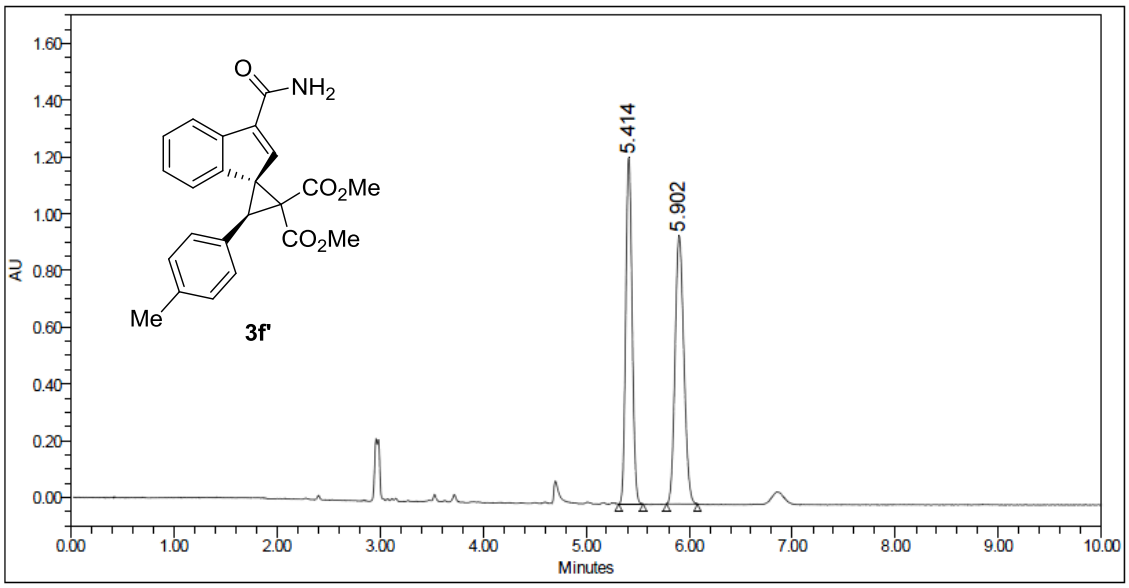

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.435 | 97.28 |
| 2 | 2.562 | 2.72 |



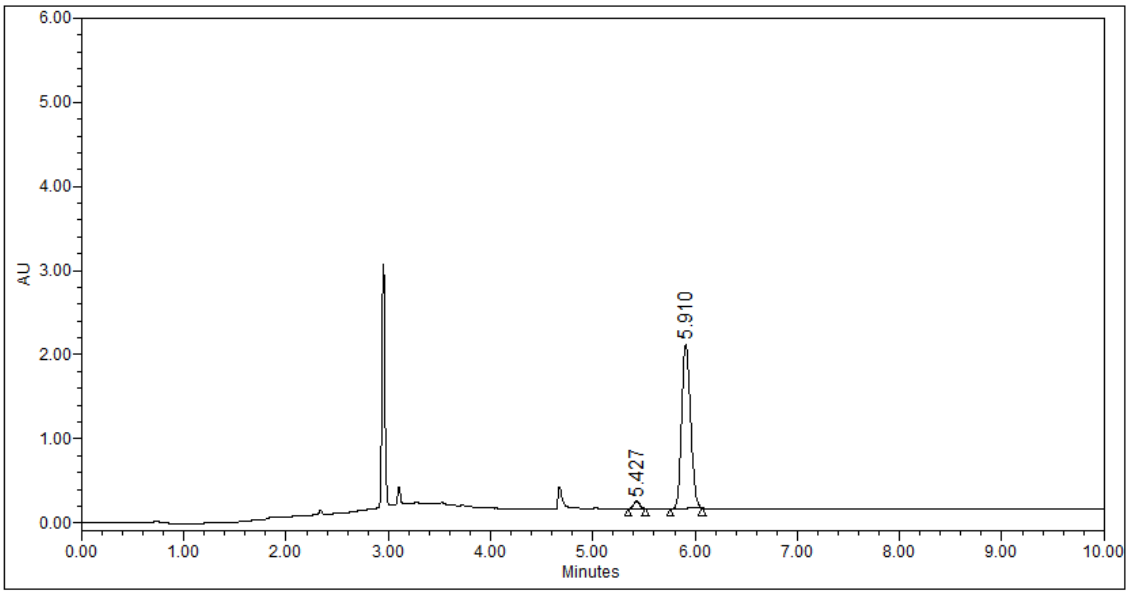

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.671 | 50.80 |
| 2 | 2.785 | 49.20 |



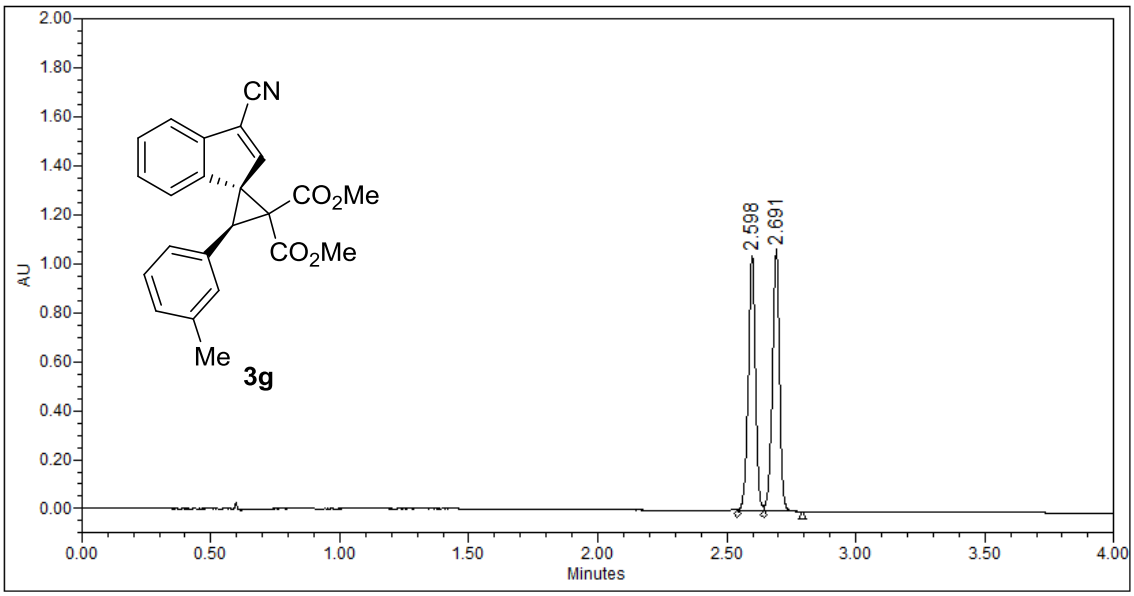

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.579 | 97.47 |
| 2 | 2.741 | 2.53 |



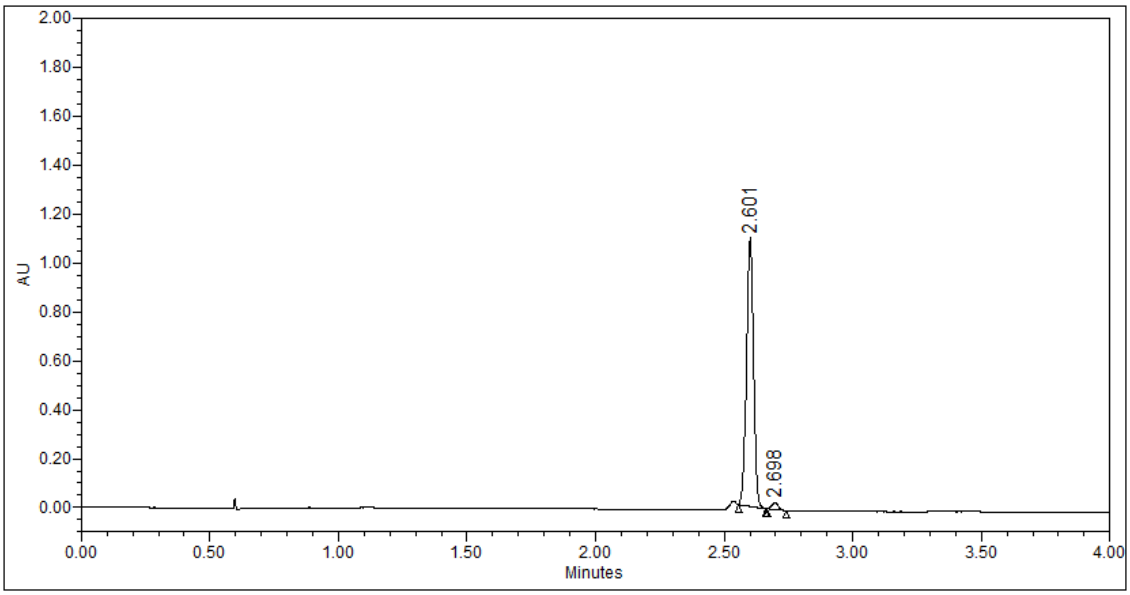

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.414 | 48.22 |
| 2 | 5.902 | 51.78 |



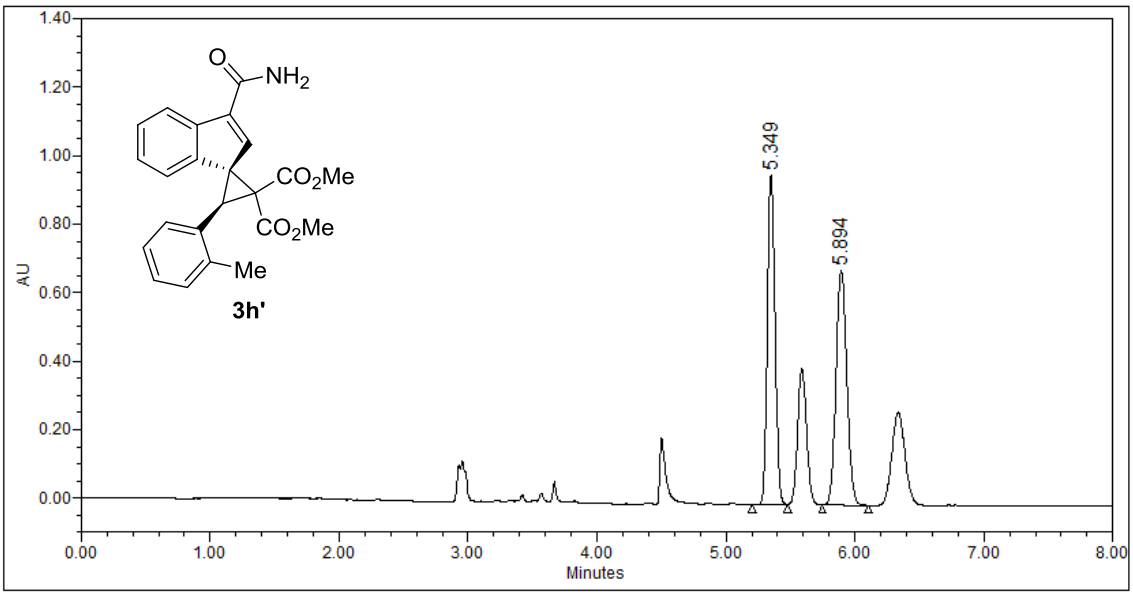

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.427 | 2.84 |
| 2 | 5.910 | 97.16 |



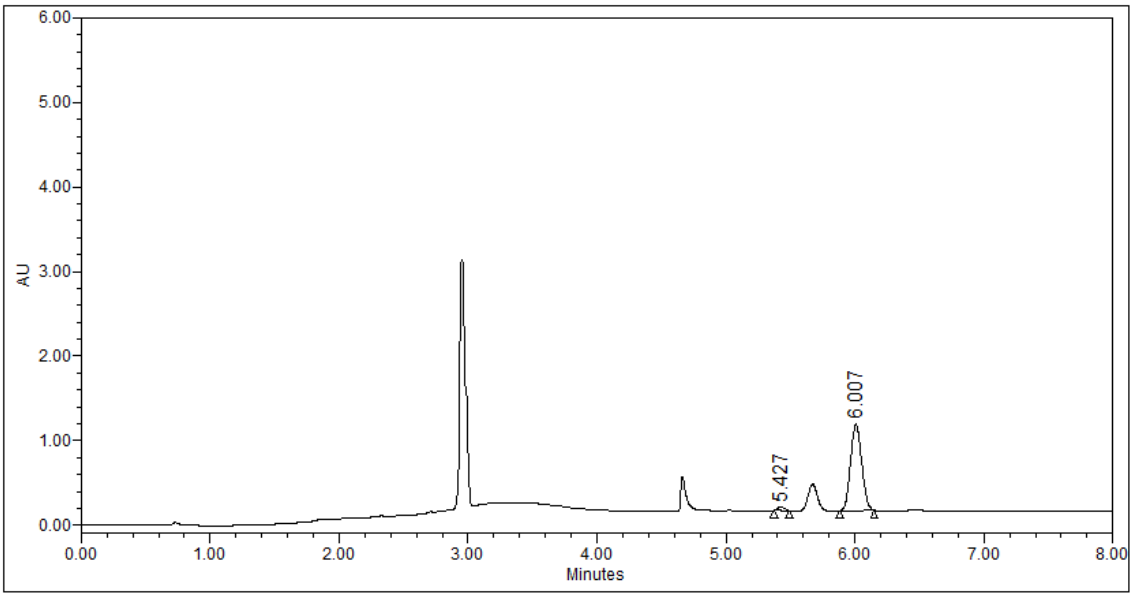

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.598 | 49.49 |
| 2 | 2.691 | 50.51 |



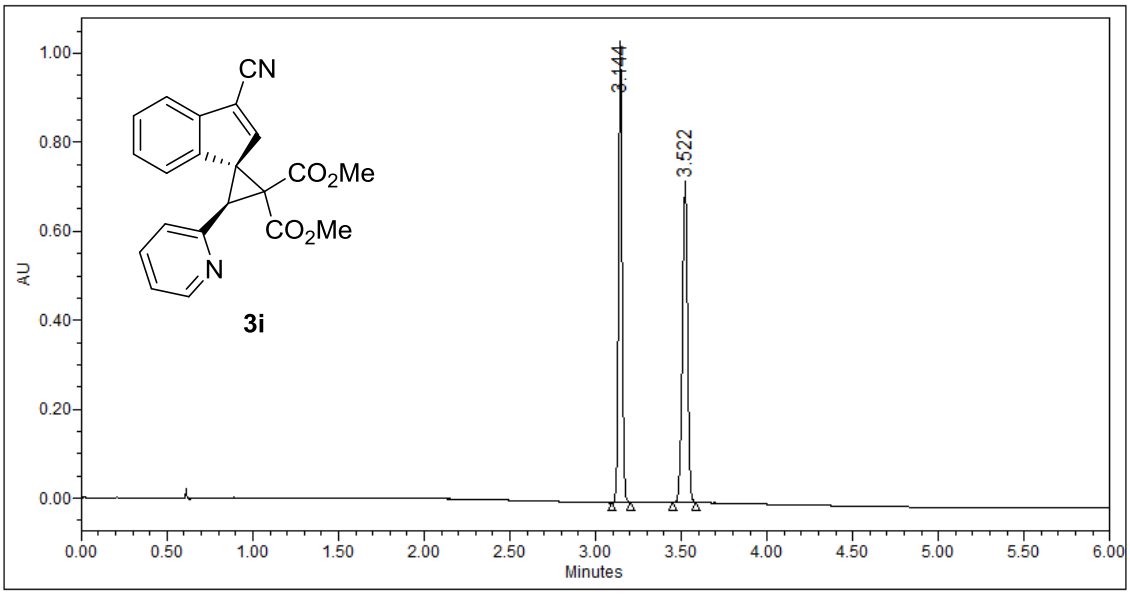

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.601 | 97.68 |
| 2 | 2.698 | 2.32 |



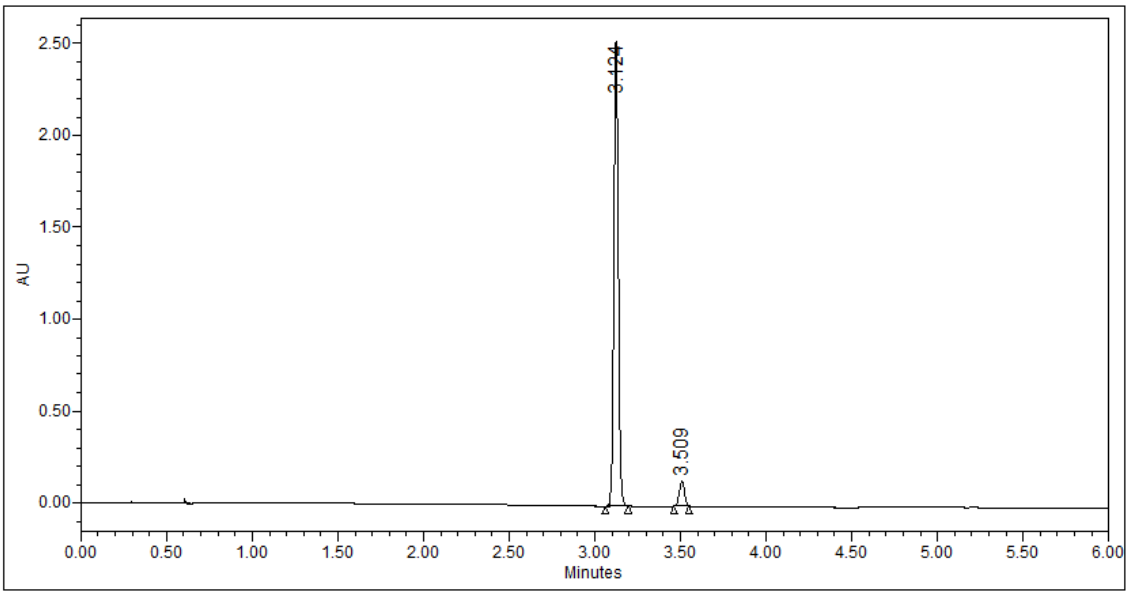

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.349 | 49.81 |
| 2 | 5.894 | 50.19 |



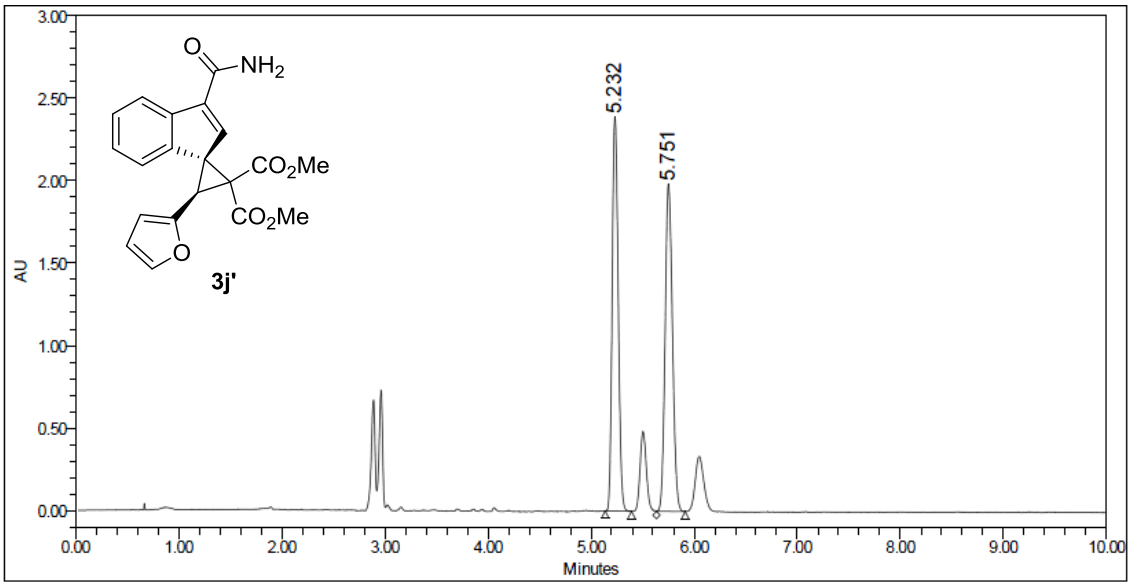

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.427 | 2.27 |
| 2 | 6.007 | 97.73 |



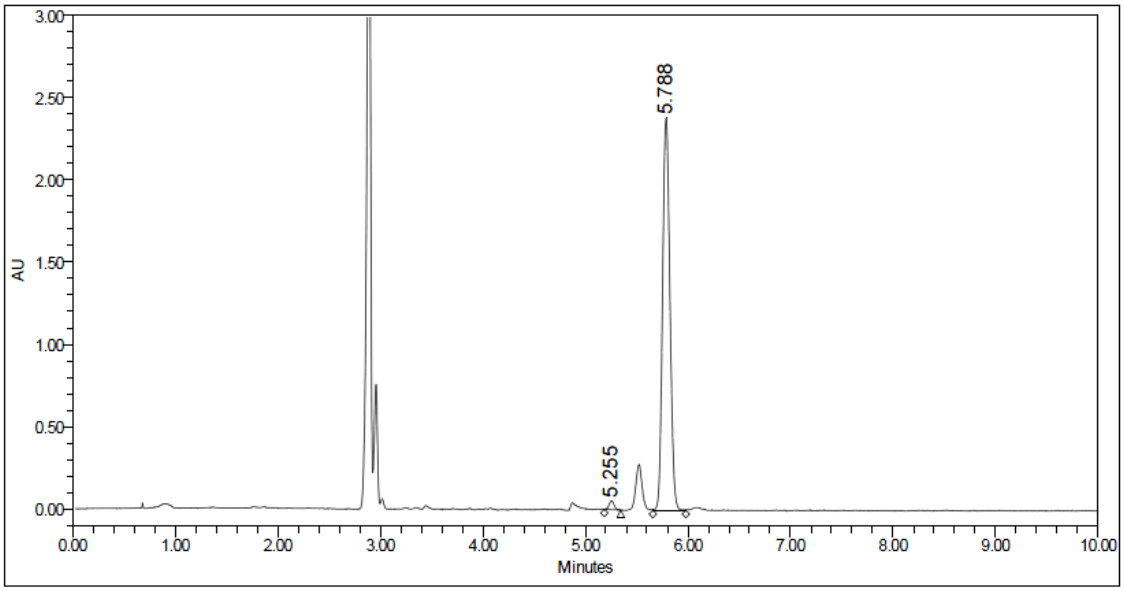

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.144 | 49.97 |
| 2 | 3.522 | 50.03 |



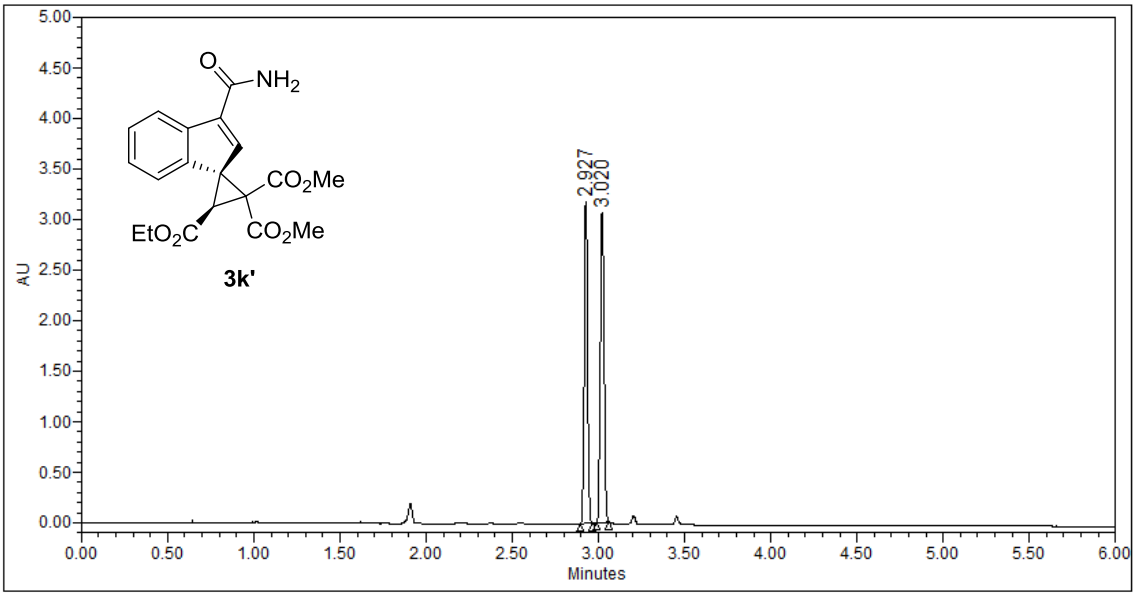

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.124 | 94.12 |
| 2 | 3.509 | 5.88 |



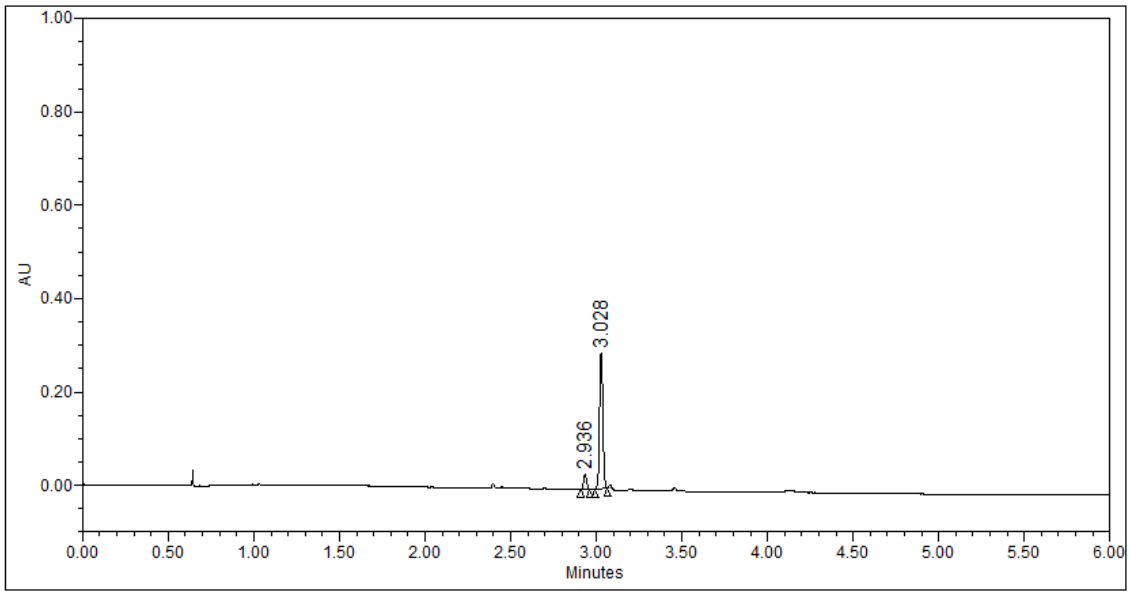

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.232 | 49.50 |
| 2 | 5.751 | 50.50 |



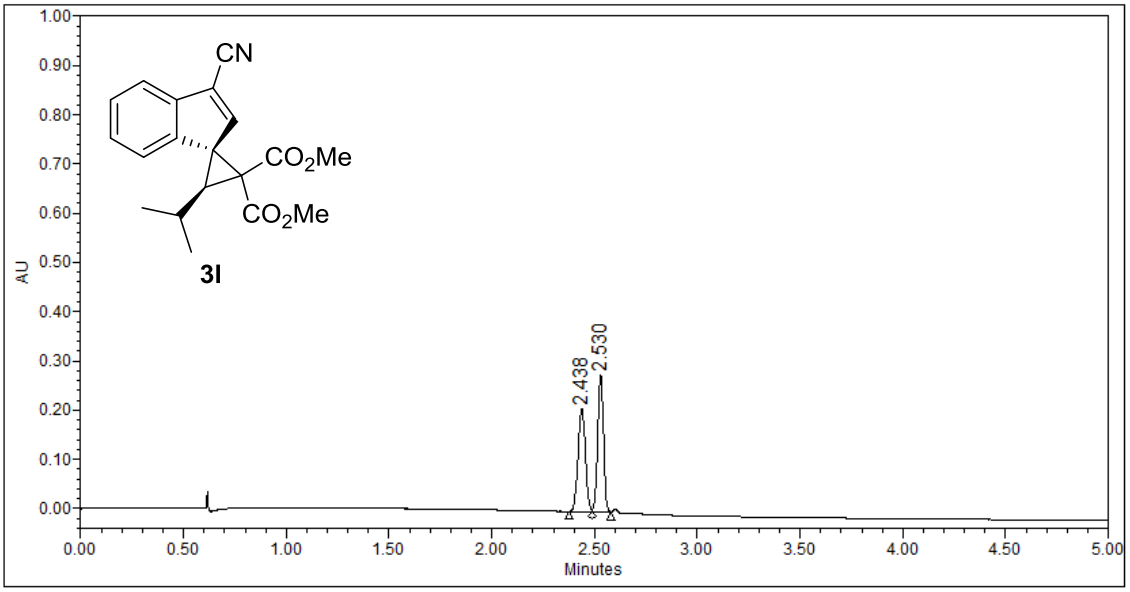

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 5.255 | 1.53 |
| 2 | 5.788 | 98.47 |



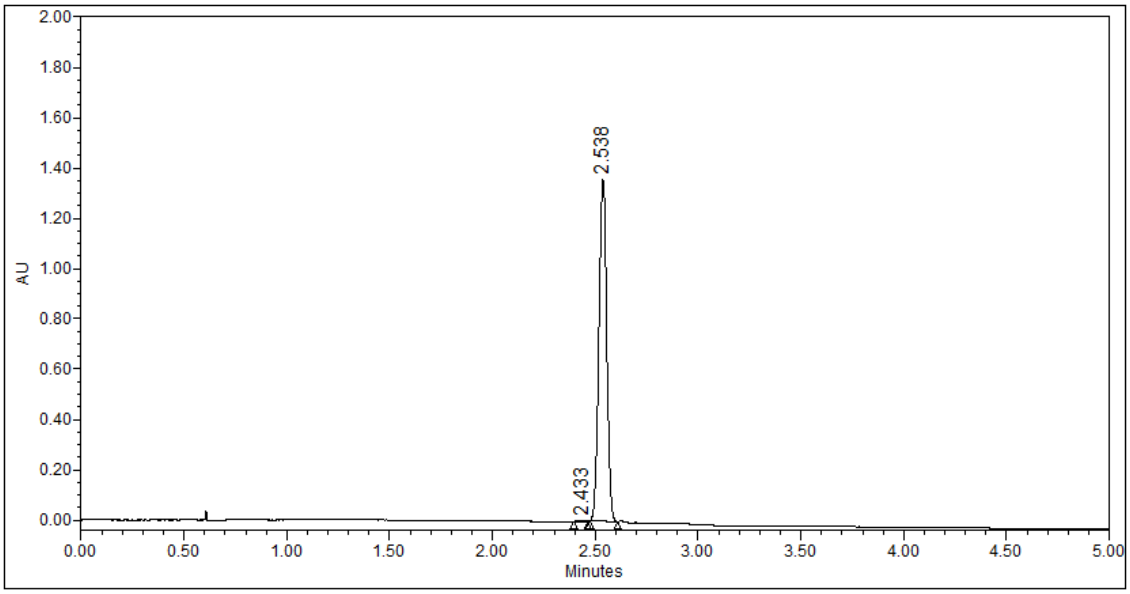

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.927 | 49.23 |
| 2 | 3.020 | 50.77 |



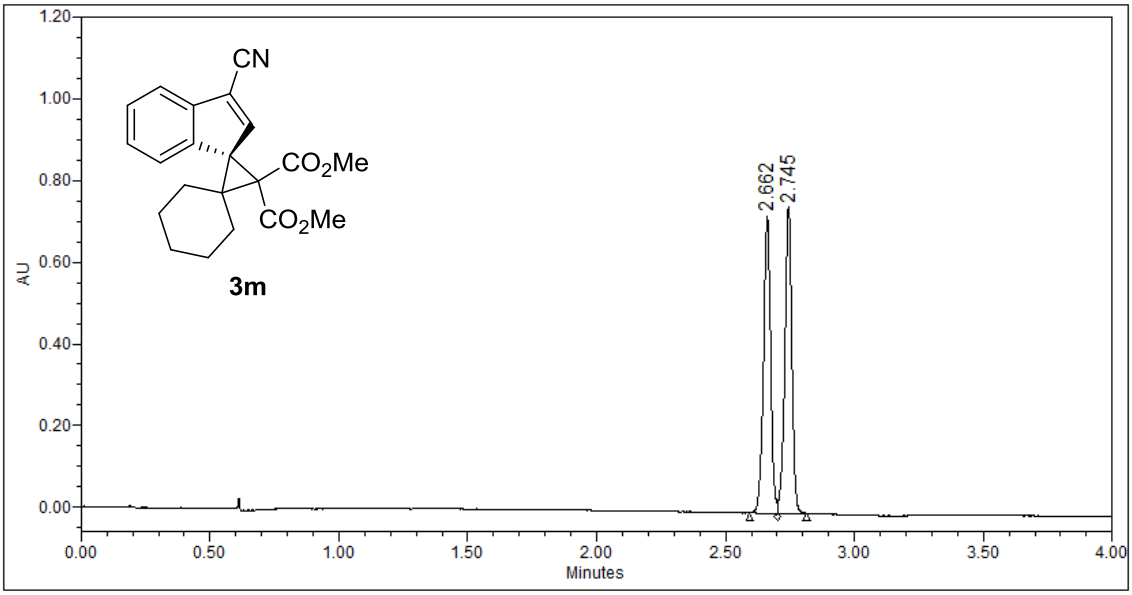

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.936 | 9.42 |
| 2 | 3.028 | 90.58 |



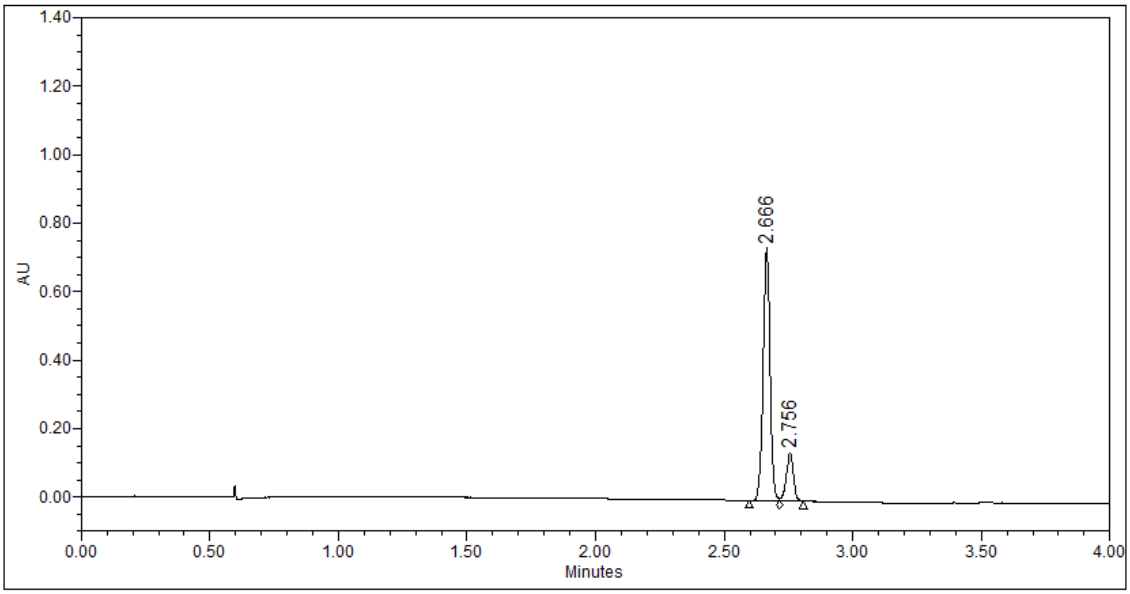

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.438 | 48.91 |
| 2 | 2.530 | 51.09 |



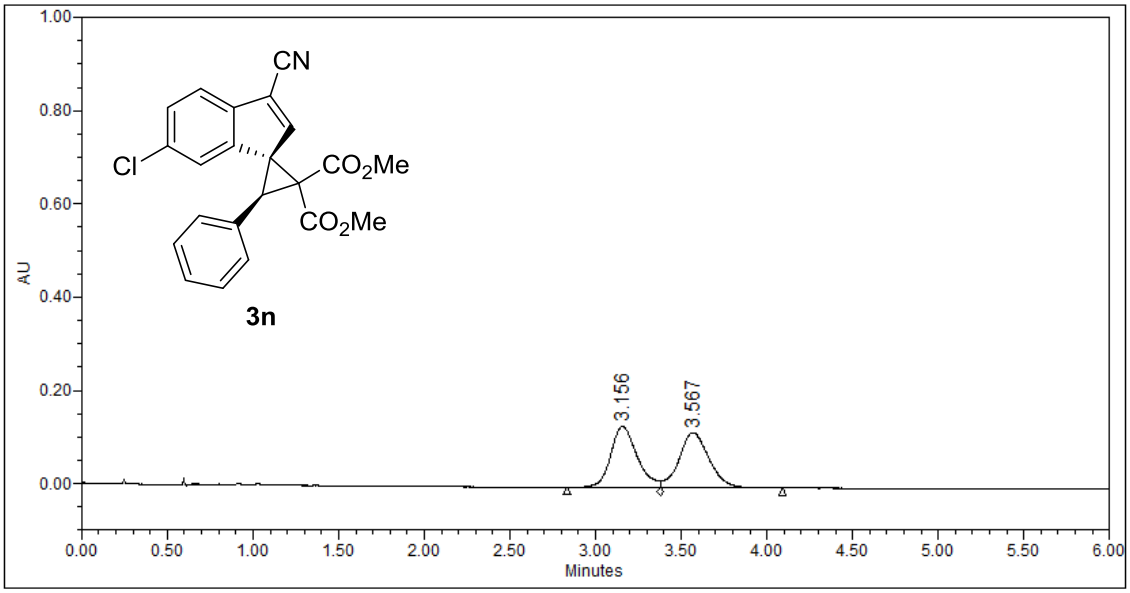

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.433 | 0.28 |
| 2 | 2.538 | 99.72 |



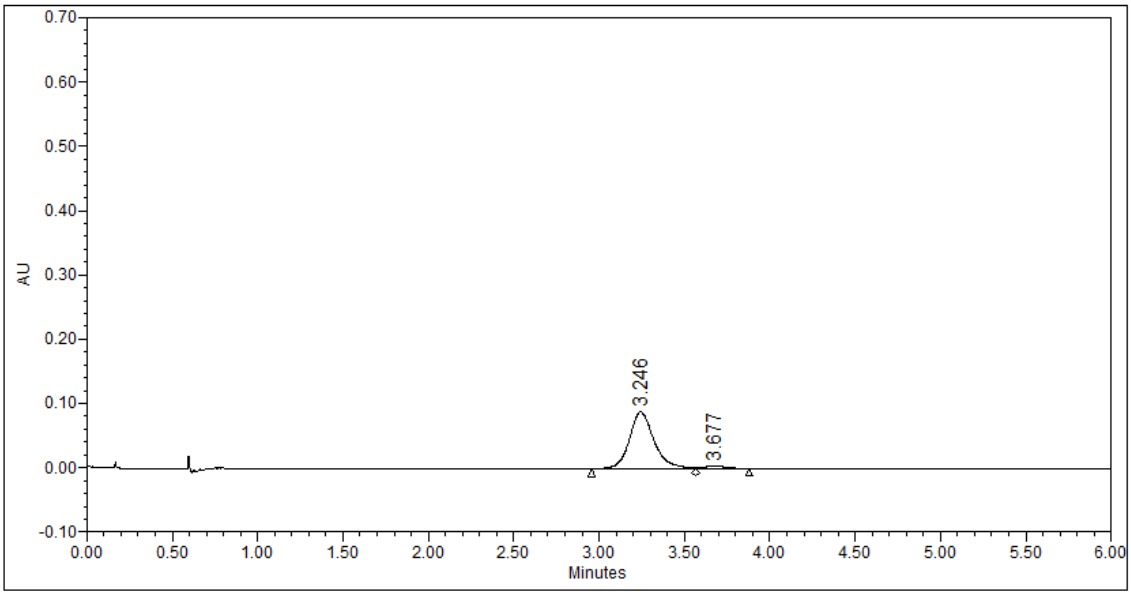

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.662 | 49.53 |
| 2 | 2.745 | 50.47 |



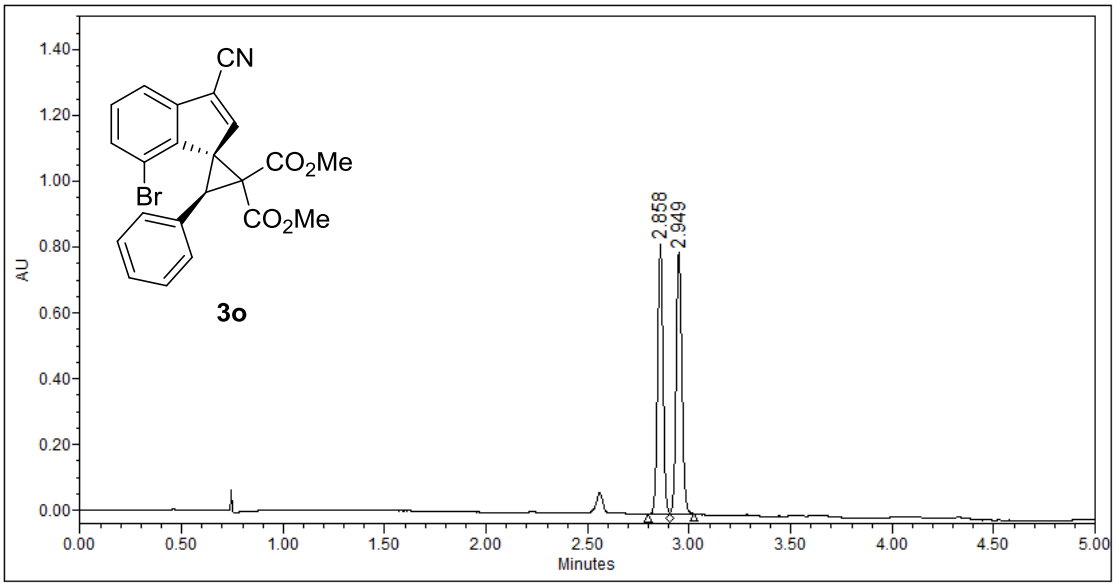

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.666 | 83.87 |
| 2 | 2.756 | 16.13 |



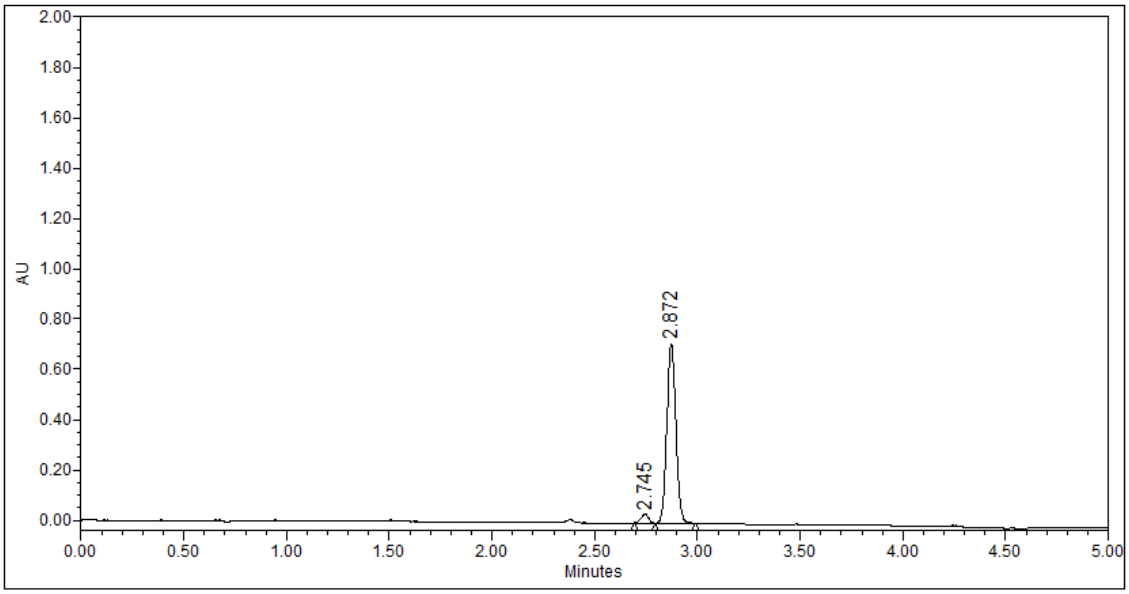

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.156 | 49.45 |
| 2 | 3.567 | 50.55 |



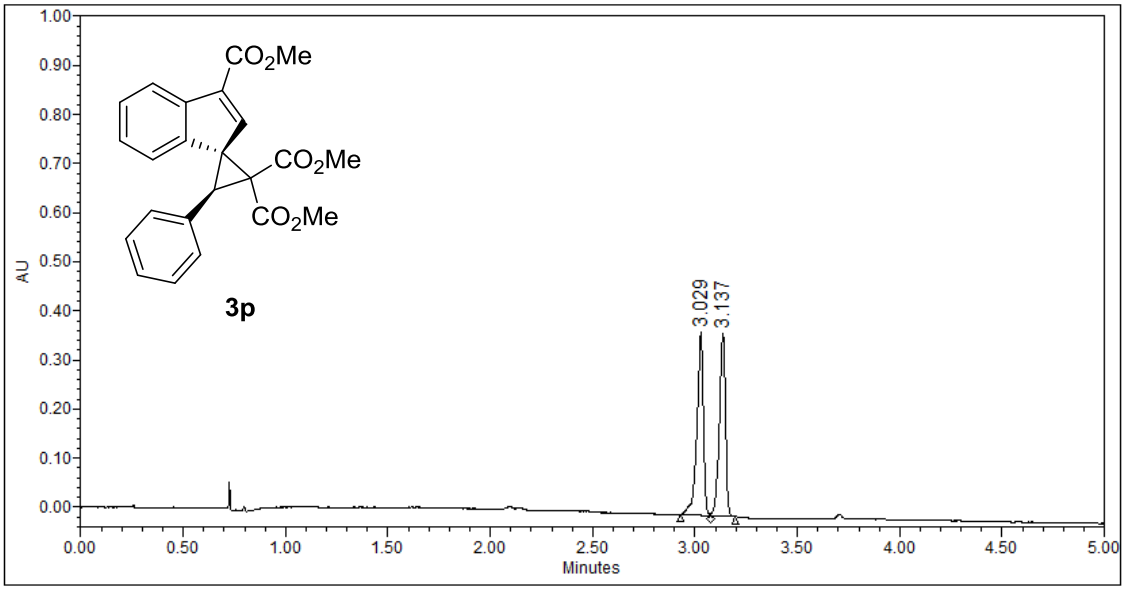

| " | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.246 | 96.02 |
| 2 | 3.677 | 3.98 |



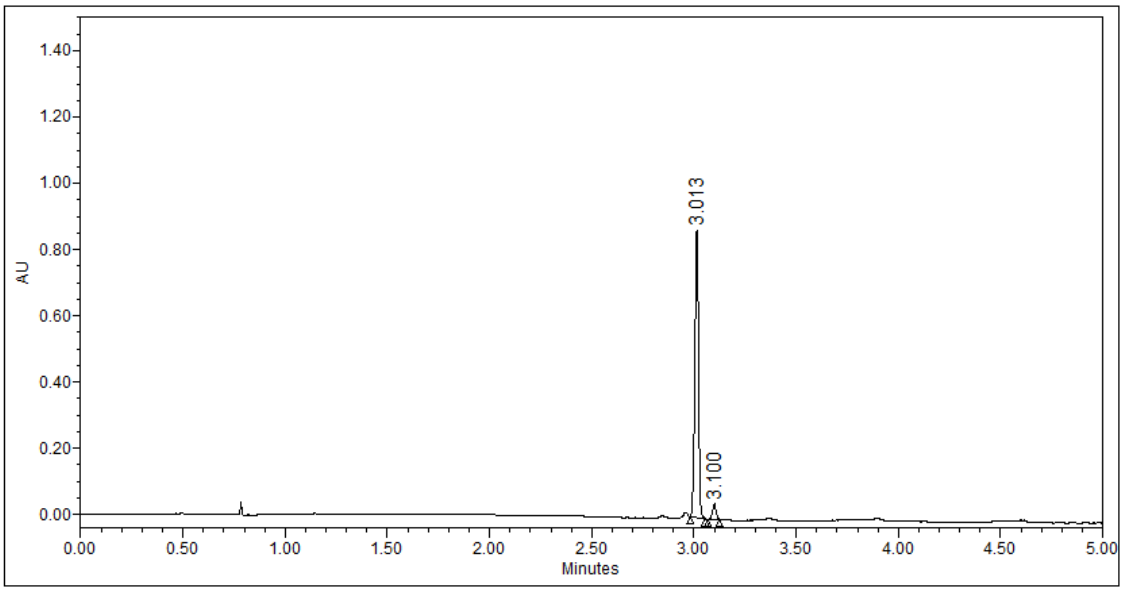

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.858 | 49.21 |
| 2 | 2.949 | 50.79 |



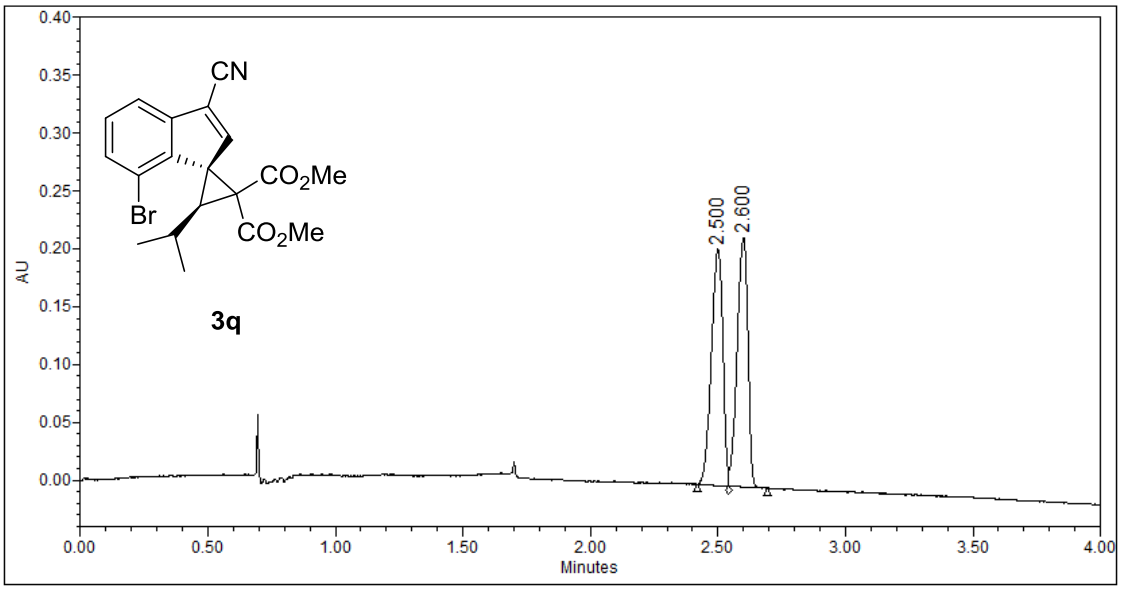

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.745 | 3.91 |
| 2 | 2.872 | 96.09 |



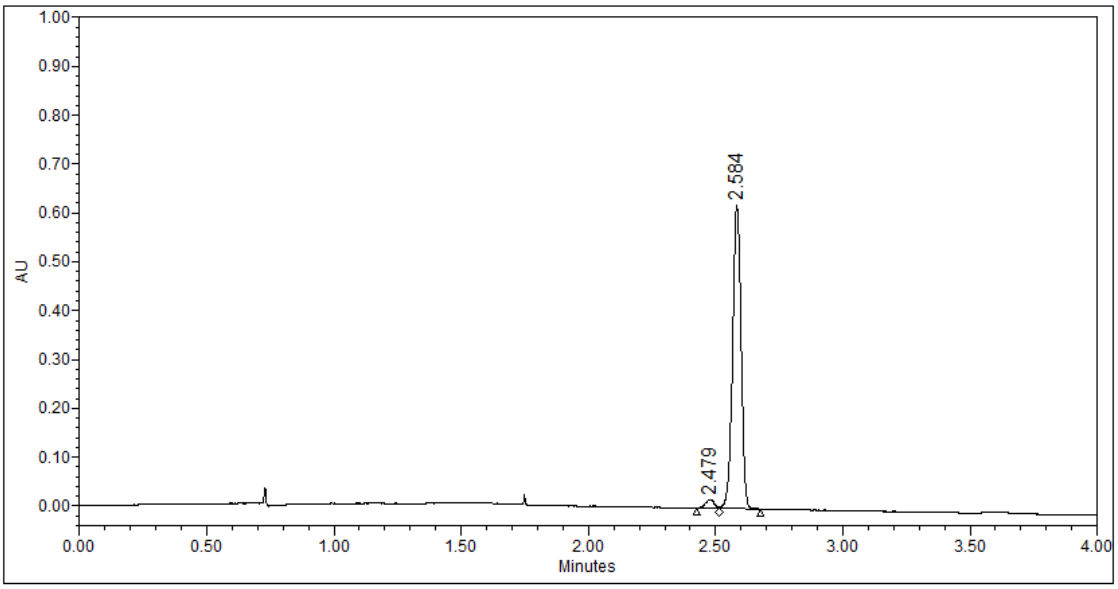

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.029 | 51.90 |
| 2 | 3.137 | 48.10 |



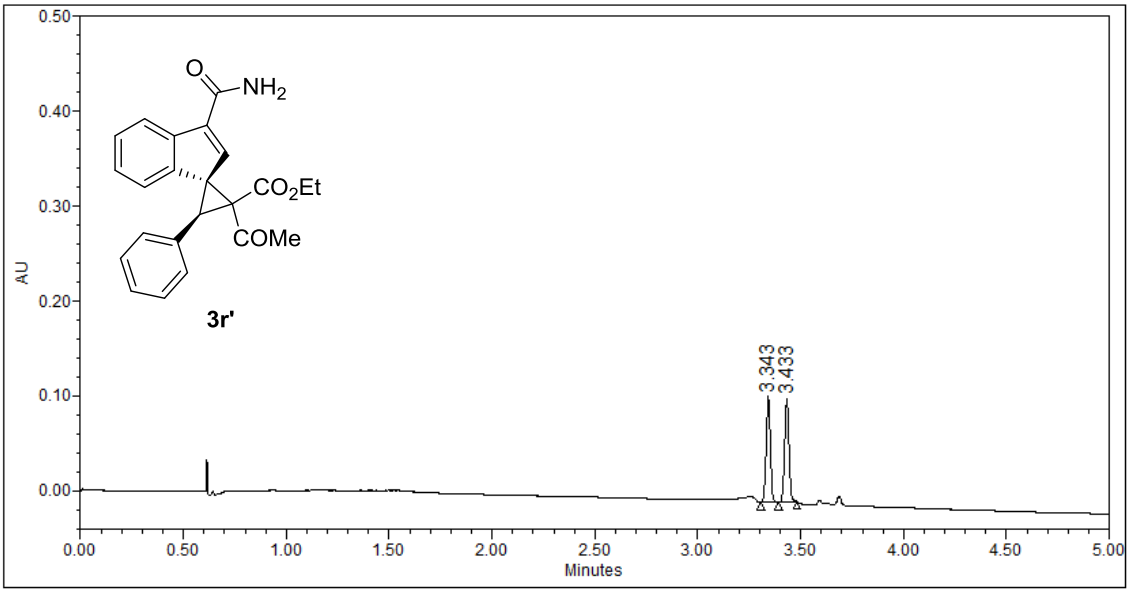

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.013 | 95.00 |
| 2 | 3.100 | 5.00 |



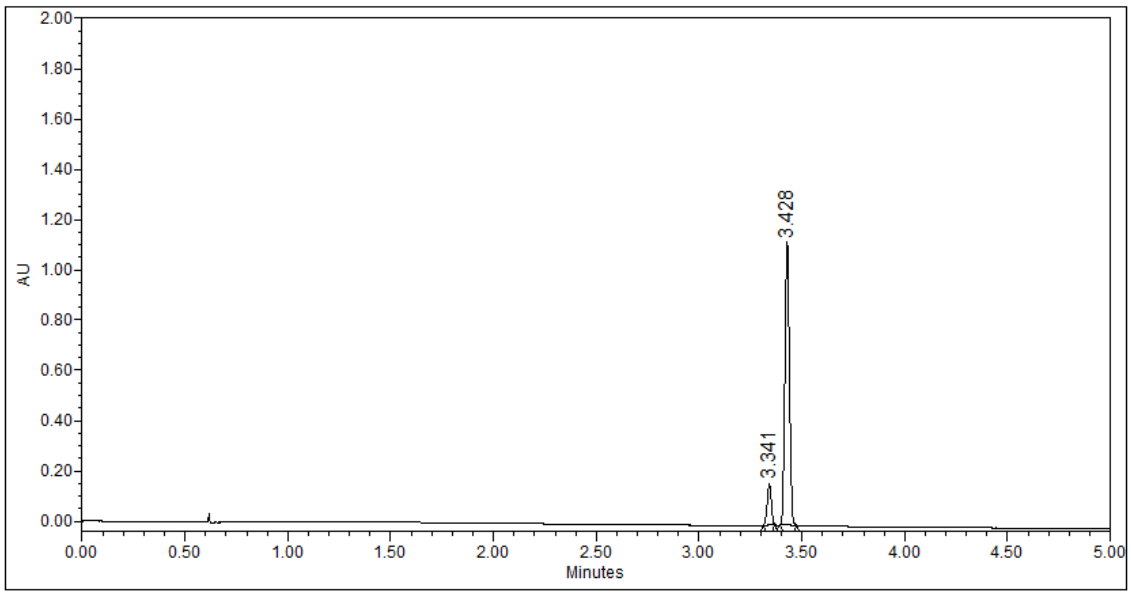

| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.500 | 50.16 |
| 2 | 2.600 | 49.84 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 2.479 | 2.73 |
| 2 | 2.584 | 97.27 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.343 | 49.51 |
| 2 | 3.433 | 50.49 |




| | Retention Time (min) | % Area |
|---|---|---|
| 1 | 3.341 | 11.85 |
| 2 | 3.428 | 88.15 |